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=> d his full

     (FILE 'HOME' ENTERED AT 13:11:39 ON 12 APR 2005)

     FILE 'HCAPLUS' ENTERED AT 13:14:28 ON 12 APR 2005
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                E DE98-98113415/AP,PRN
                E DE98-19813415/AP,PRN
L2            1 SEA ABB=ON  PLU=ON  WO98-EP7876#/AP,PRN
L3            2 SEA ABB=ON  PLU=ON  (L1 OR L2)

     FILE 'REGISTRY' ENTERED AT 13:18:00 ON 12 APR 2005

     FILE 'HCAPLUS' ENTERED AT 13:18:02 ON 12 APR 2005
L4              TRA L3 1- RN :       14 TERMS

     FILE 'REGISTRY' ENTERED AT 13:18:03 ON 12 APR 2005
L5           14 SEA ABB=ON  PLU=ON  L4

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L6            4 SEA ABB=ON  PLU=ON  (WO98-EP7876# OR DE97-19753681#)/AP,PRN

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L7         1773 SEA ABB=ON  PLU=ON  ERYTHROPOIETIN#

     FILE 'HCAPLUS' ENTERED AT 13:27:24 ON 12 APR 2005
L8              QUE ABB=ON  PLU=ON  L7 OR ERYTHROPOIETIN# OR EP OR EPO OR
                EPOETIN# OR EPOGIS# OR HEMOPOIETIN#
L9              QUE ABB=ON  PLU=ON  (L7 OR ERYTHROPOIETIN# OR EP OR EPO OR
                EPOETIN# OR EPOGIS# OR HEMOPOIETIN#) (L) PREP+NT/RL
                E HELA/CT
                E E4+ALL
                E E2
                E E3+ALL
L10        10836 SEA ABB=ON  PLU=ON  HELA CELL+OLD,NT/CT
L11            6 SEA ABB=ON  PLU=ON  L10 (L) L8
L12           16 SEA ABB=ON  PLU=ON  L10 AND L9
L13           18 SEA ABB=ON  PLU=ON  L11 OR L12
                E BURG J/AU
L14           60 SEA ABB=ON  PLU=ON  ("BURG J"/AU OR "BURG J A R"/AU OR "BURG J
                G"/AU OR "BURG J LAUWRENCE"/AU OR "BURG J LAWRENCE"/AU OR
                "BURG J P"/AU OR "BURG J R"/AU OR "BURG J T"/AU OR "BURG J
                W"/AU)
                E BURG JOSEF/AU
L15           12 SEA ABB=ON  PLU=ON  "BURG JOSEF"/AU
                E SELLINGER K/AU
L16           10 SEA ABB=ON  PLU=ON  ("SELLINGER K H"/AU OR "SELLINGER KARL
                HEINZ"/AU)
                E HASSELBECK A/AU
                E HASELBECK A/AU
L17           29 SEA ABB=ON  PLU=ON  ("HASELBECK A"/AU OR "HASELBECK ANTON"/AU)

                E KOLL HANS/AU
L18           22 SEA ABB=ON  PLU=ON  ("KOLL HANS"/AU OR "KOLL HANS GERD"/AU OR
                "KOLL HANS PETER"/AU)
                E SELLINGER H/AU
L19         3198 SEA ABB=ON  PLU=ON  (BOEHRINGER (1A) MANNHEIM)/CS,PA
L20            3 SEA ABB=ON  PLU=ON  L13 AND (L14 OR L15 OR L16 OR L17 OR L18
                OR L19)
L21           15 SEA ABB=ON  PLU=ON  L13 NOT L20
                SEL AN L21 2 8-9 11 14
L22            5 SEA ABB=ON  PLU=ON  ("118:33948"/AN OR "129:157543"/AN OR
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                48"/AN OR "1998:429257"/AN OR "2000:800657"/AN OR "2001:152816"
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L24             QUE ABB=ON  PLU=ON  L8 OR (D24.185.348.453.240.150. OR
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              D12.776.395.240.150.  OR D24.611.350.400.442.240.150.)/CT
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L26         168 SEA ABB=ON  PLU=ON  L24 AND L25
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L28           9 SEA ABB=ON  PLU=ON  L27 AND L25
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              D TRI TOT
              D AB L28 TOT
              SEL AN L28 1-7 9
L29           8 SEA ABB=ON  PLU=ON  (1998316650/AN OR 2000076248/AN OR
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              95403327/AN OR 97012216/AN) AND L28

=> b hcap
FILE 'HCAPLUS' ENTERED AT 14:06:47 ON 12 APR 2005
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FILE COVERS 1907 - 12 Apr 2005  VOL 142 ISS 16
FILE LAST UPDATED: 11 Apr 2005  (20050411/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


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L20  ANSWER 1 OF 3  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   1999:96350  HCAPLUS
DN   130:149562
ED   Entered STN:  12 Feb 1999
TI   Production of erythropoietin by endogenous gene activation of human cells
IN   Stern, Anne; Brandt, Michael; Honold, Konrad; Auer, Johannes; Koll,
     Hans
PA   Boehringer Mannheim G.m.b.H., Germany
SO   PCT Int. Appl., 70 pp.
     CODEN: PIXXD2
DT   Patent
LA   German
IC   ICM  C12N015-12
     ICS  C12N015-85; C12N015-62; C12N015-90; C12N005-10; C07K014-505;
          A61K038-18
CC   3-2 (Biochemical Genetics)
     Section cross-reference(s): 16
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             DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG,
             KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
             NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
             UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
             CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
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	AU 754619	B2	20021121		
	ZA 9806515	A	20000124	ZA 1998-6515	19980722
	ZA 9806516	A	20000124	ZA 1998-6516	19980722
	EP 986644	A1	20000322	EP 1998-941401	19980722
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	JP 2001511343	T2	20010814	JP 2000-504243	19980722
	TW 574372	B	20040201	TW 1998-87116028	19980924
	WO 9928455	A1	19990610	WO 1998-EP7819	19981202
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	ZA 9811003	A	20000602	ZA 1998-11003	19981202
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	JP 2001525342	T2	20011211	JP 2000-523332	19981202
	JP 3394240	B2	20030407		
	JP 2003180392	A2	20030702	JP 2002-321415	19981202
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	AU 9921581	A1	19990616	AU 1999-21581	19981203
	AU 744086	B2	20020214		
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	BR 9813391	A	20001010	BR 1998-13391	19981203
	TR 200001580	T2	20001221	TR 2000-200001580	19981203
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	US 6391633	B1	20020521	US 2000-463380	20000121
	US 6555373	B1	20030429	US 2000-607277	20000630
	US 6673575	B1	20040106	US 2000-555533	20000905
	US 2002110913	A1	20020815	US 2001-985357	20011102
	US 6544748	B2	20030408		
	AU 2002029337	A5	20020523	AU 2002-29337	20020328
	AU 776280	B2	20040902		
	US 2004203001	A1	20041014	US 2003-351397	20030127
	US 2003166275	A1	20030904	US 2003-353767	20030129
	JP 2004339234	A2	20041202	JP 2004-219290	20040727
PRAI	EP 1997-112640	A	19970723		
	DE 1997-19753681	A	19971203		
	US 1998-113692	A	19980710		
	EP 1998-113415	A	19980717		
	EP 1997-121073	A	19971201		
	EP 1998-113409	A	19980717		
	WO 1998-EP4590	W	19980722		
	JP 2000-523332	A3	19981202		
	WO 1998-EP7819	W	19981202		
	JP 2000-523237	A3	19981203		
	WO 1998-EP7876	W	19981203		
	US 2000-463380	A1	20000121		
	US 2001-985357	A1	20011102		

CLASS PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9905268	ICM	C12N015-12
	ICS	C12N015-85; C12N015-62; C12N015-90; C12N005-10; C07K014-505; A61K038-18
WO 9905268	ECLA	C07K014/505; C12N015/10; C12N015/62A
DE 19753681	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B
US 6548296	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B
WO 9928455	ECLA	C07K014/505; C12P021/00B
WO 9928346	ECLA	C07K014/505
US 6391633	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B
US 6555373	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B
US 6673575	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B
US 2002110913	ECLA	C07K014/505; C12N015/10; C12P021/00B; C12N015/62A
US 2004203001	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B
US 2003166275	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B
JP 2004339234	FTERM	4B064/AG18; 4B064/CA10; 4B064/CA19; 4B064/CC24; 4B064/CD09; 4B064/CE06; 4B064/CE10; 4B064/CE12; 4B064/DA03; 4C084/AA02; 4C084/BA01; 4C084/BA09; 4C084/BA34; 4C084/CA56; 4C084/DB56; 4C084/NA05; 4C084/NA14; 4C084/ZA552; 4H045/AA10; 4H045/AA20; 4H045/AA30; 4H045/BA10; 4H045/BA53; 4H045/CA40; 4H045/DA13; 4H045/EA24; 4H045/FA74; 4H045/GA10; 4H045/GA15; 4H045/GA24; 4H045/GA25; 4H045/GA26

AB The invention concerns human cells which, owing to the activation of the endogenous human erythropoietin gene, can produce erythropoietin (EPO) in sufficient quantities and degree of purity to allow human EPO to be economically produced as a pharmaceutical preparation The invention also concerns a process for producing such human EPO-producing cells, DNA-constructs for activating the endogenous EPO gene in human cells and a process for the large-scale production of EPO in human cells. A HeLa S3 cell containing erythropoietin genes fused to a cytomegalovirus immediate early promoter and enhancer was produced by homologous recombination. Optimization of the erythropoietin gene expression involved alteration of the signal sequence, shortening of the distance between the cytomegalovirus promoter and translation start site, and amplification of the gene. A recombinant cell line producing >7000 ng erythropoietin/mL/106 cells/24 h was obtained. The erythropoietin was purified by a series of chromatog. steps (affinity, hydrophobic interaction, hydroxyapatite, reverse phase HPLC) to produce erythropoietin with specific activity >100,000 units/mg.

ST erythropoietin manuf recombinant human cell cytomegalovirus immediate early promoter

IT Animal cell line
(HT-1080; production of erythropoietin by endogenous gene activation of human cells)

IT Animal cell line
(Namalwa; production of erythropoietin by endogenous gene activation of human cells)

IT **HeLa cell**
(S3; production of **erythropoietin** by endogenous gene activation of human cells)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(for erythropoietin, activation of; production of erythropoietin by endogenous gene activation of human cells)

IT Recombination, genetic
(homologous; production of erythropoietin by endogenous gene activation of human cells)

IT Animal cell
(human; production of erythropoietin by endogenous gene activation of human cells)

IT Promoter (genetic element)
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(immediate early, of cytomegalovirus, for activation of erythropoietin gene; production of erythropoietin by endogenous gene activation of human

cells)
IT Plasmid vectors
(p189; production of erythropoietin by endogenous gene activation of human cells)
IT Fermentation
(production of erythropoietin by endogenous gene activation of human cells)
IT Genetic element
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(signal sequence, modified; production of erythropoietin by endogenous gene activation of human cells)
IT Promoter (genetic element)
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(viral, for activation of erythropoietin gene; production of erythropoietin by endogenous gene activation of human cells)
IT 75432-66-5, Blue Sepharose
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(Blue Sepharose; production of erythropoietin by endogenous gene activation of human cells)
IT 9002-03-3P, Dihydrofolate reductase
RL: **BPN (Biosynthetic preparation)**; BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); **PREP (Preparation)**; PROC (Process)
(gene for, as amplification gene; production of **erythropoietin** by endogenous gene activation of human cells)
IT 62213-36-9P, Neomycin phosphotransferase
RL: **BPN (Biosynthetic preparation)**; BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); **PREP (Preparation)**; PROC (Process)
(gene for, as selectable marker; production of **erythropoietin** by endogenous gene activation of human cells)
IT **11096-26-7P, Erythropoietin**
RL: **BPN (Biosynthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(production of **erythropoietin** by endogenous gene activation of human cells)
IT 72980-05-3
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(production of erythropoietin by endogenous gene activation of human cells)
IT 220271-95-4 220271-96-5 220271-97-6 220271-98-7
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(signal peptide N-terminus; production of erythropoietin by endogenous gene activation of human cells)
RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Applied Research Systems; WO 9109955 A 1991 HCAPLUS
(2) Boehringer Mannheim Gmbh; WO 9635718 A 1996 HCAPLUS
(3) Cangene Corp; WO 9619573 A 1996 HCAPLUS
(4) Cell Genesys Inc; EP 0747485 A 1996 HCAPLUS
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(7) Krystal, G; Blood 1986, V67(1), P71 HCAPLUS
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(12) Transkaryotic Therapies Inc; WO 9412650 A 1994 HCAPLUS
(13) Transkaryotic Therapies Inc; WO 9531560 A 1995 HCAPLUS
(14) Transkaryotic Therapies Inc; WO 9629411 A 1996 HCAPLUS

L20 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:96349 HCAPLUS
DN 130:149561

ED Entered STN: 12 Feb 1999
TI Identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines
IN Brandt, Michael; Franze, Reinhard; Pessara, Ulrich
PA Boehringer Mannheim G.m.b.H., Germany
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA German
IC ICM C12N015-12
ICS C12N015-85; C12N015-10; C07K014-505
CC 3-2 (Biochemical Genetics)
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9905267	A1	19990204	WO 1998-EP4584	19980722
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	AU 737605	B2	20010823		
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	ZA 9806516	A	20000124	ZA 1998-6516	19980722
	EP 1000154	A1	20000517	EP 1998-942592	19980722
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	TR 200000140	T2	20000522	TR 2000-200000140	19980722
	BR 9811542	A	20000822	BR 1998-11542	19980722
	JP 2001511342	T2	20010814	JP 2000-504242	19980722
	MX 200000677	A	20001109	MX 2000-677	20000119
	US 6395484	B1	20020528	US 2000-463339	20000530
	US 6555373	B1	20030429	US 2000-607277	20000630
	AU 2002029337	A5	20020523	AU 2002-29337	20020328
	AU 776280	B2	20040902		
	US 2002164792	A1	20021107	US 2002-112755	20020402
	US 6846673	B2	20050125		
	US 2004203001	A1	20041014	US 2003-351397	20030127
PRAI	EP 1997-112640	A	19970723		
	EP 1997-121073	A	19971201		
	US 1998-113692	A	19980710		
	DE 1997-19753681	A	19971203		
	WO 1998-EP4584	W	19980722		
	US 2000-463339	A1	20000530		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9905267	ICM	C12N015-12
	ICS	C12N015-85; C12N015-10; C07K014-505
WO 9905267	ECLA	C07K014/505; C12N015/10
US 6548296	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B
US 6395484	ECLA	C07K014/505; C12N015/10; C12N015/62A
US 6555373	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B
US 2002164792	ECLA	C07K014/505; C12N015/10; C12N015/62A
US 2004203001	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B

AB A process for selecting human cells for the production of human proteins by endogenous gene activation allows human proteins to be produced in economically feasible quantities and in a form suitable for producing a pharmaceutical composition The human cells should contain the gene with the desired nucleotide sequence and should undergo at least 5 population doublings within 14 days in suspension culture and serum-free medium. Ideally, the cells should also contain >2 copies of the target gene, produce the protein with the appropriate glycosylation, and be free of infectious contaminants. Also disclosed are recombinant human cell lines containing an endogenous gene operatively fused to a heterologous promoter as

well as a process for producing human proteins in such cell lines. Using the above techniques, a HeLa S3 cell containing erythropoietin genes fused to a cytomegalovirus immediate early promoter and enhancer was produced. This recombinant cell line produced >7000 ng erythropoietin/mL/106 cells/24 h.

ST human cell line heterologous promoter protein manuf; erythropoietin manuf recombinant HeLa cell cytomegalovirus early promoter

IT Animal cell line
(HT-1080; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Animal cell line
(Namalwa; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT **HeLa cell**
(S3; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(activation of; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Promoter (genetic element)
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(heterologous; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Proteins, general, preparation
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(human; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Animal cell line
Fermentation
(identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Blood-coagulation factors
Bone morphogenetic proteins
Chemokines
Enkephalins
Hedgehog protein
Interferons
Interleukins
Neurotrophic factors
Receptors
Transforming growth factors
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Cytomegalovirus
(immediate early promoter and enhancer of; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Promoter (genetic element)
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(immediate early, of cytomegalovirus; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Plasmid vectors
(p179, for activation of erythropoietin gene; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Plasmid vectors

(p187, for activation of erythropoietin gene; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)
IT Plasmid vectors
(p189, for activation of erythropoietin gene; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)
IT Plasmid vectors
(p190, for activation of erythropoietin gene; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)
IT Plasmid vectors
(p192, for activation of erythropoietin gene; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)
IT 9002-60-2P, ACTH, preparation 9002-72-6P, Growth hormone 9014-42-0P, Thrombopoietin **11096-26-7P, Erythropoietin**
60118-07-2P, Endorphin 62683-29-8P, Colony-stimulating factor
RL: **BPN (Biosynthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Cell Genesys Inc; EP 0747485 A 1996 HCAPLUS
(2) Genetics Inst; EP 0411678 A 1991 HCAPLUS
(3) Integrated Genetics Inc; EP 0267678 A 1988 HCAPLUS
(4) Sumitomo Chemical Co; EP 0232034 A 1987 HCAPLUS
(5) Transkaryotic Therapies Inc; WO 9309222 A 1993 HCAPLUS
(6) Transkaryotic Therapies Inc; WO 9412650 A 1994 HCAPLUS
(7) Transkaryotic Therapies Inc; WO 9531560 A 1995 HCAPLUS
(8) Transkaryotic Therapies Inc; WO 9629411 A 1996 HCAPLUS

L20 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:96346 HCAPLUS
DN 130:149560
ED Entered STN: 12 Feb 1999
TI Introduction of mutant genes into human cells by homologous recombination and production of mutant human proteins with the resulting recombinant cells
IN Stern, Anne; Honold, Konrad
PA Boehringer Mannheim G.m.b.H., Germany
SO PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DT Patent
LA German
IC ICM C12N015-00
CC 3-2 (Biochemical Genetics)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9905264	A2	19990204	WO 1998-EP4583	19980722
	WO 9905264	A3	19990422		
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9890673	A1	19990216	AU 1998-90673	19980722
	AU 729489	B2	20010201		
	ZA 9806517	A	20000124	ZA 1998-6517	19980722
	EP 1000167	A2	20000517	EP 1998-942591	19980722
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	BR 9811531	A	20000822	BR 1998-11531	19980722
	TR 200000172	T2	20001221	TR 2000-200000172	19980722
	JP 2001511341	T2	20010814	JP 2000-504239	19980722
	MX 200000645	A	20001027	MX 2000-645	20000118

	US 2002068318	A1	20020606	US 2000-463338	20000121
	US 6444441	B2	20020903		
	US 2002177195	A1	20021128	US 2002-194244	20020715
PRAI	EP 1997-112639	A	19970723		
	WO 1998-EP4583	W	19980722		
	US 2000-463338	A1	20000121		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9905264	ICM	C12N015-00
WO 9905264	ECLA	C12N015/10B; C12N015/90B
US 2002068318	ECLA	C12N015/10B; C12N015/90B
US 2002177195	ECLA	C12N015/10B; C12N015/90B

AB A process is disclosed for producing mutant forms of eukaryotic proteins with recombinant eukaryotic cells. Also disclosed is a process for producing the recombinant human cells by a process of homologous recombination. Finally, the invention concerns the human cells produced by this process and the mutant human proteins obtained therefrom, as well as pharmaceutical compns. containing these mutant proteins. Thus, a targeting vector was prepared which contained a 5'-flanking region of the tissue plasminogen activator (tPA) gene, a Rous sarcoma virus promoter-neomycin phosphotransferase gene chimera, an SV40 early promoter-dihydrofolate reductase gene chimera, the cytomegalovirus promoter, a fragment of the tPA gene comprising the coding region for the signal peptide and the first 3 amino acids of the mature tPA, and a part of intron G of the tPA gene. HeLa cells were transfected with this DNA by electroporation and vector-containing cells were selected with G418. Recombinant HeLa cells secreting tPA mutein into the medium were produced.

ST recombinant human cell homologous recombination mutein prodn; tissue plasminogen activator mutein manuf HeLa cell

IT Animal cell line
(HT-1080; introduction of mutant genes into human cells by homologous recombination and production of mutant human proteins with resulting recombinant cells)

IT Animal cell line
(Namalwa; introduction of mutant genes into human cells by homologous recombination and production of mutant human proteins with resulting recombinant cells)

IT Recombination, genetic
(homologous; introduction of mutant genes into human cells by homologous recombination and production of mutant human proteins with resulting recombinant cells)

IT **HeLa cell**
Molecular cloning
(introduction of mutant genes into human cells by homologous recombination and production of mutant human proteins with resulting recombinant cells)

IT Interleukin receptors
Interleukins
Proteins, specific or class
Tumor necrosis factors
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(muteins; introduction of mutant genes into human cells by homologous recombination and production of mutant human proteins with resulting recombinant cells)

IT Cytomegalovirus
(promoter of; introduction of mutant genes into human cells by homologous recombination and production of mutant human proteins with resulting recombinant cells)

IT Promoter (genetic element)
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(viral; introduction of mutant genes into human cells by homologous recombination and production of mutant human proteins with resulting recombinant cells)

IT 9002-03-3P, Dihydrofolate reductase
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PREP

(Preparation); PROC (Process)
(gene for, as amplification gene; introduction of mutant genes into human cells by homologous recombination and production of mutant human proteins with resulting recombinant cells)

IT 62213-36-9P, Neomycin phosphotransferase
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation); PROC (Process)
(gene for, recombinant cell selection with; introduction of mutant genes into human cells by homologous recombination and production of mutant human proteins with resulting recombinant cells)

IT 9004-10-8DP, Insulin, mutein, preparation **11096-26-7DP, Erythropoietin**, mutein 139639-23-9DP, Tissue plasminogen activator, mutein
RL: **BPN (Biosynthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(introduction of mutant genes into human cells by homologous recombination and production of mutant human proteins with resulting recombinant cells)

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L23 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2004:333871 HCAPLUS
DN 140:351724
ED Entered STN: 23 Apr 2004
TI Sequence of human interleukin-18 binding protein (IL-18BP) promoter and regulation of IL-18BP gene
IN Novick, Daniela; Rubinstein, Menachem; Hurgin, Vladimir
PA Yeda Research and Development Co. Ltd, Israel
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-65
CC 3-4 (Biochemical Genetics)
Section cross-reference(s): 1, 13, 15
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2004033694	A2	20040422	WO 2003-IL815	20031009
	WO 2004033694	A3	20040527		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI IL 2002-152232 A 20021010
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2004033694	ICM	C12N015-65

AB The present invention relates to the DNA sequence of human interleukin-18 binding protein (IL-18BP) promoter. IL-18BP was constitutively produced in monocytes and macrophages and was induced by IFNγ, in monocytes and in many different cells. Induction of IL-18BP by IFNγ was further enhanced by the addition of IL-6 and TNFα. Exptl. result confirmed the importance of IRF-1 as a mediator of basal as well as IFNγ-induced expression of IL 18BP. The results obtained with EMSA indicated that upon induction with IFNγ, IRF-1 binds to the IRF-E element in the IL-18BP promoter. In addition, a complex comprising IRF-1 and C/EBPβ was formed and bound to the GAS element.

ST interleukin 18 binding protein human promoter sequence; gene IL18BP regulation IFNgamma IRF1 CEBPbeta IL6

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(AP-1 (activator protein 1), mutated at site for, in promoter; sequence of human interleukin-18 binding protein (IL-18BP) promoter and regulation of IL-18BP gene)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(C/EBP-β (CCAAT box/enhancer element-binding protein β); sequence of human interleukin-18 binding protein (IL-18BP) promoter and its therapeutic uses)
IT Animal cell line
(CHO, as host; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT Animal cell line
(COS, as host; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT Animal cell line
(CV-1, as host; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT Genetic element
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GAS; sequence of human interleukin-18 binding protein (IL-18BP) promoter and its therapeutic uses)
IT Animal cell line
(Hep G2, as host; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IL-18BP; sequence of human interleukin-18 binding protein (IL-18BP) promoter and regulation of IL-18BP gene)
IT Enhancer (genetic element)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(IRF-E; sequence of human interleukin-18 binding protein (IL-18BP) promoter and its therapeutic uses)
IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(ISGF-2 (interferon-stimulated gene factor 2); sequence of human interleukin-18 binding protein (IL-18BP) promoter and its therapeutic uses)
IT Lipoprotein receptors
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(LDL, hsLDLR, expression of; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT Proteins
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(TNF receptor binding proteins, expression of; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT Mus
(Transgenic; sequence of human interleukin-18 binding protein (IL-18BP) promoter and its therapeutic uses)
IT Animal cell line
(U937, as host; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT Animal cell line
(WISH lymphoblast, as host; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT Transcriptional regulation
(activation; sequence of human interleukin-18 binding protein (IL-18BP) promoter and regulation of IL-18BP gene)
IT **HeLa cell**
(as host; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT Granulomatous disease
(chronic, treatment of; sequence of human interleukin-18 binding protein (IL-18BP) promoter and its therapeutic uses)
IT Hematopoiesis
(disorders, treatment of; sequence of human interleukin-18 binding

protein (IL-18BP) promoter and its therapeutic uses)
IT Antibodies and Immunoglobulins
Interleukin 18
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(expression of; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT Retroviral vectors
Viral vectors
(for expression of heterologous gene; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT Interleukin 6
Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(induction of IL-18BP by; sequence of human interleukin-18 binding protein (IL-18BP) promoter and its therapeutic uses)
IT Proteins
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(interleukin-18 binding protein (IL-18BP); sequence of human interleukin-18 binding protein (IL-18BP) promoter and regulation of IL-18BP gene)
IT Genetic element
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(intron; sequence of human interleukin-18 binding protein (IL-18BP) promoter and regulation of IL-18BP gene)
IT Animal cell
(mammalian, as host; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT Transplant and Transplantation
(of mammalian cell with vectors comprising IL-18BP promoter; sequence of human interleukin-18 binding protein (IL-18BP) promoter and its therapeutic uses)
IT Anti-AIDS agents
Gene therapy
(sequence of human interleukin-18 binding protein (IL-18BP) promoter and its therapeutic uses)
IT DNA sequences
Human
(sequence of human interleukin-18 binding protein (IL-18BP) promoter and regulation of IL-18BP gene)
IT Promoter (genetic element)
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(sequence of human interleukin-18 binding protein (IL-18BP) promoter and regulation of IL-18BP gene)
IT Molecular cloning
(sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT Immunodeficiency
(severe combined, treatment of; sequence of human interleukin-18 binding protein (IL-18BP) promoter and its therapeutic uses)
IT Hematopoietic precursor cell
Macrophage
Monocyte
(transduction of, with vectors comprising IL-18BP promoter; sequence of human interleukin-18 binding protein (IL-18BP) promoter and its therapeutic uses)
IT Thalassemia
(treatment of; sequence of human interleukin-18 binding protein (IL-18BP) promoter and its therapeutic uses)
IT Adeno-associated virus
Feline immunodeficiency virus
Human immunodeficiency virus 1
Human spumavirus
Murine leukemia virus
Vesicular stomatitis virus
(vector for expression of heterologous gene; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)

IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ, induction of IL-18BP by; sequence of human interleukin-18 binding protein (IL-18BP) promoter and its therapeutic uses)
IT 9002-61-3P, Chorionic gonadotropin 9002-68-0P, Follicle-stimulating hormone 9002-72-6P, Growth hormone 9014-00-0P, Luciferase **11096-26-7P, Erythropoietin** 139639-23-9P, Tissue-type plasminogen activator 143011-72-7P, Granulocyte colony stimulating factor
RL: **BPN (Biosynthetic preparation)**; BSU (Biological study, unclassified); BIOL (Biological study); **PREP (Preparation)**
(expression of; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT 9054-89-1P
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(manganese-dependent, expression of; sequence of human interleukin-18 binding protein (IL-18BP) promoter for expression of heterologous gene)
IT 681524-25-4 681524-26-5 681524-27-6 681524-28-7 681524-29-8
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(nucleotide sequence; sequence of human interleukin-18 binding protein (IL-18BP) promoter and its therapeutic uses)
IT 681525-86-0
RL: PRP (Properties)
(unclaimed nucleotide sequence; sequence of human interleukin-18 binding protein (IL-18BP) promoter and regulation of IL-18BP gene)
IT 681525-73-5 681525-74-6 681525-75-7 681525-76-8 681525-77-9
681525-78-0 681525-79-1 681525-80-4 681525-81-5 681525-82-6
681525-83-7 681525-84-8 681525-85-9
RL: PRP (Properties)
(unclaimed sequence; sequence of human interleukin-18 binding protein (IL-18BP) promoter and regulation of IL-18BP gene)

L23 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2003:610640 HCAPLUS
DN 139:160799
ED Entered STN: 08 Aug 2003
TI Methods and vectors for optimizing protein production and homogeneity in mammalian cells
IN Beach, David H.; Wang, Jenny
PA Genetica, Inc., USA
SO PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-63
ICS C12P019-34
CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 6, 7, 16
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2003064659	A1	20030807	WO 2003-US844	20030113

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2002-347601P P 20020111
CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2003064659	ICM	C12N015-63
	ICS	C12P019-34

Search done by Noble Jarrell

AB Methods and vectors for optimizing protein production in mammalian cells are provided. The present invention further provides cultures of cells wherein protein expression across the culture of cells is more homogeneous.

ST cloning protein fermn homogeneity mammal cell

IT Cell membrane
(-associated protein; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Animal cell line
(293; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Animal cell line
(3T3; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Proteins
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(A; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Hybridoma
(B-cell; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Animal cell line
(BHK; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Proteins
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(CD; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Animal cell line
(CHO-K1; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Animal cell line
(CHO; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Animal cell line
(COS; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Proteins
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(D; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Animal cell line
(HEK; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Animal cell line
(Hep G2; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Genetic element
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(IRES (internal ribosomal entry site) element, in vector; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Proteins
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(Ig like; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Animal cell line
(MIDCK; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Animal cell line
(REW138; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Animal cell line
(Vero; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Proteins
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(addressins; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Plasmid vectors
(copy number; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Phenotypes
(flow cytometry for selection of subpopulation of cells showing desired; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Cytometry
(flow, for selection of subpopulation of cells showing desired phenotype; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Genetic markers
(fluorecence-generating, for co-selection of gene encoding protein; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Fluorometry
(for selection of gene encoding protein; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Proteins
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(green fluorescent; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Antibodies and Immunoglobulins
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(heavy chain; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Chromatin
(heterochromatin, -mediated gene silencing inhibitors, production of; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Drug delivery systems
(immunotoxins; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Mutation
(in protein; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Post-transcriptional processing
(interference; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Peptides, preparation
Proteins
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(intracellular or cell surface-associated; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Viral vectors
(lentivirus; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Antibodies and Immunoglobulins
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(light chain; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Antibiotic resistance
(marker for selection of desired gene encoding protein; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Proteins
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(membrane; methods and vectors for optimizing protein production and homogeneity in mammalian cells)
IT Animal tissue culture

Culture media
Genetic engineering
HeLa cell
Human
Mammalia
Molecular cloning
Mus
Pulmonary surfactant
Retroviral vectors
(methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Antibodies and Immunoglobulins
Antigens
Antisense RNA
Blood-coagulation factors
Cytokines
Double stranded RNA
Enzymes, preparation
Growth factor receptors
Growth factors, animal
Hemopoietins
Homing receptors
Hormone receptors
Insulin-like growth factor-binding proteins
Integrins
Interferons
Interleukins
Lipoproteins
Lymphotoxin
Macrophage inflammatory protein 1α
Neurotrophic factors
Platelet-derived growth factors
RANTES (chemokine)
RNA
Rheumatoid factors
TCR (T cell receptors)
Transforming growth factors
Transport proteins
Tumor necrosis factors
mRNA
RL: **BPN (Biosynthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Antibodies and Immunoglobulins
RL: BPN (Biosynthetic preparation); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Antibodies and Immunoglobulins
RL: BPN (Biosynthetic preparation); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(monoclonal; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Growth factors, animal
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(osteoglycins; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Fermentation
Microorganism
(protein; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Proteins
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(regulatory; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Transcriptional regulation
(repression, heterochromatin-mediated, inhibitor production; methods and

vectors for optimizing protein production and homogeneity in mammalian cells)

IT Toxins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(resistance marker for selection of desired gene encoding protein; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Albumins, preparation
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(serum; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Nutrients
(supplied for selection of desired protein in complex medium; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Lentivirus
(vector; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT Retrotransposon
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(vector; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT 9002-69-1P, Relaxin
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(A or B chain; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT 96098-73-6P, Enkephalinase
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(enkephalinase; methods and vectors for optimizing protein production and homogeneity in mammalian cells)

IT 9001-27-8P, Factor VIII 9001-28-9P, Factor IX 9001-98-3P, Rennin 9002-04-4P, Thrombin 9002-64-6P, Parathyroid hormone 9002-67-9P, Luteinizing hormone 9002-68-0P, Follicle stimulating hormone 9002-71-5P, Thyroid stimulating hormone 9002-72-6P, Somatotropin 9003-98-9P, DNASe 9004-10-8P, Insulin, preparation 9007-12-9P, Calcitonin 9007-92-5P, Glucagon, preparation 9026-81-7P, Nuclease 9034-39-3P, Growth hormone releasing factor 9035-58-9P, Blood-coagulation factor III 9035-68-1P, ProInsulin 9041-92-3P, α1 Antitrypsin 9054-89-1P, Superoxide dismutase
11096-26-7P, Erythropoietin 31362-50-2P, Bombesin 57285-09-3P, Inhibin 62031-54-3P, Fgf 62229-50-9P, Egf 62683-29-8P, Csf 67763-96-6P, IGF-I 67763-97-7P, Insulin like growth factor 2 80497-65-0P, Muellerian-inhibiting hormone 85637-73-6P, Atrial natriuretic factor 87004-01-1P, Prorelaxin 99085-47-9P, Decay accelerating factor 105913-11-9P, Plasminogen activator 107666-54-6P, GnRH-associated peptide 109319-16-6P, Factor VIII 112540-84-8P, 4-70-Insulin-like growth factor I (human reduced) 114949-22-3P, Activin 127464-60-2P, Vascular endothelial growth factor
RL: **BPN (Biosynthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(methods and vectors for optimizing protein production and homogeneity in mammalian cells)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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L23 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2002:676210 HCAPLUS
DN 137:196695
ED Entered STN: 08 Sep 2002
TI Eukaryotic cell cultures with improved protein production characteristics by activation of NF-kappa-B transcription factor complex
IN Price, Virginia L.; Wong-Madden, Sharon T.

PA Immunex Corporation, USA
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-85
ICS C12N005-10; C07K014-47; C12P021-02
CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 9, 16
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002068668	A2	20020906	WO 2002-US5652	20020222
	WO 2002068668	A3	20030501		
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	US 2002127654	A1	20020912	US 2002-80428	20020222
PRAI	US 2001-270943P	P	20010222		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2002068668	ICM	C12N015-85
	ICS	C12N005-10; C07K014-47; C12P021-02
US 2002127654	ECLA	C07K014/47A1B; C12N015/85; C12P021/02

AB The invention is in the field of eukaryotic cell culture, and provides improved methods of recombinant protein production More specifically, the invention relates to the activation of the NF-κB signaling pathway in cultured cells so as to obtain cell cultures with advantageous properties. The invention is based, in part, on the discovery that activation of the NF-κB transcription factor complex leads to increased expression of a recombinant gene of interest. Accordingly, in one aspect, the invention provides an eukaryotic host cell genetically engineered to activate the NF-κB transcription factor complex, and to express a protein of interest as an extracellular product. Preferred NF-κB transcription factors are p65, p50, cRel, p52 and RelB. The protein of interest can be any recombinant protein of economic interest.

ST eukaryotic cell culture protein prodn NFkappaB activation

IT Animal cell line
(293; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Animal cell line
(3T3; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Apolipoproteins
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(A-I; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Animal cell line
(BHK; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT CD antigens
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(CD27; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor

complex)

IT Glycoproteins
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(CD40-L (antigen CD40 ligand), soluble; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Animal cell line
(CHO; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Adenoviridae
Cytomegalovirus
Rous sarcoma virus
Simian virus 40
(CMV, promoter from; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Animal cell line
(COS; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Animal cell line
(CV-1; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Apolipoproteins
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(E; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT **Hemopoietins**
RL: **BPN (Biosynthetic preparation)**; BUU (Biological use, unclassified); **PUR (Purification or recovery)**; BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(FLT3 ligand, soluble; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Fusion proteins (chimeric proteins)
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(Fc-fusion; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Animal cell line
(MDCK; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Transcription factors
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(NF-κB (nuclear factor of κ light chain gene enhancer in B-cells), p65 mutant, caspase resistant; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Transcription factors
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(NF-κB (nuclear factor of κ light chain gene enhancer in B-cells), p65, p50, cRel, p52 and RelB; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Antigens
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)

(OX-40; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Animal cell line
(PC12; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Cytokine receptors
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(RANK (receptor activator of NF-κB); eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Proteins
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(TRAIL (tumor necrosis factor-related apoptosis-inducing ligand); eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Cytokine receptors
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(TRAIL, soluble; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Animal cell line
(Vero; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Animal cell line
(WI-38; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Interleukin 2
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antagonist; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Peptones
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cell line growing in peptone-free medium; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Human
Multiple myeloma
(cells; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Animal tissue culture
Genetic engineering
HeLa cell
(eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Antibodies and Immunoglobulins
CD30 (antigen)
CD34 (antigen)
Cytokines
Globins
Interferons
Interleukin 15
Interleukin 2 receptors
Interleukins
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)

(eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Eukaryota
(expression host cell; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Interleukin receptors
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(interleukin 15, soluble; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Animal cell
(mammalian, expression host; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Proteins
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(of interest, expression; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Secretion (process)
(protein, of interest; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Culture media
(protein-free, host cell adapted to grow; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Genetic element
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(regulatory; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Interleukin 4 receptors
Tumor necrosis factor receptors
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(soluble; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Interleukin 1 receptors
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(type II, soluble; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT Promoter (genetic element)
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(viral; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT 207621-35-0P, RANKL
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)
(RANK ligand; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT 148047-29-4P, Gene tek protein kinase
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation); USES (Uses)

(TEK/Ork; eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

IT 9001-28-9P, Blood-coagulation factor IX 9002-64-6P, Parathyroid hormone 9002-72-6P, Growth hormone 9004-10-8P, Insulin, biological studies 9007-12-9P, Calcitonin 9007-92-5P, Glucagon, biological studies 9041-92-3P 9054-89-1P, Superoxide dismutase 9061-61-4P, Nerve growth factor **11096-26-7P**, **Erythropoietin** 37228-64-1P, Glucocerebrosidase 61912-98-9P, Insulin like growth factor 62683-29-8P, Colony stimulating factor 83869-56-1P, GM CSF 113189-02-9P, Blood-coagulation factor VIII, procoagulant 118549-37-4P, Insulinotropin 139639-23-9P, Tissue plasminogen activator
RL: **BPN (Biosynthetic preparation)**; BUU (Biological use, unclassified); **PUR (Purification or recovery)**; BIOL (Biological study); **PREP (Preparation)**; USES (Uses)
(eukaryotic cell cultures with improved protein production characteristics by activation of NF-κB transcription factor complex)

L23 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:613437 HCAPLUS
DN 136:211461
ED Entered STN: 23 Aug 2001
TI Self-complementary recombinant adeno-associated virus (scAAV) vectors promote efficient transduction independently of DNA synthesis
AU McCarty, D. M.; Monahan, P. E.; Samulski, R. J.
CS UNC Gene Therapy Center, School of Pharmacy, University of North Carolina, Chapel Hill, NC, USA
SO Gene Therapy (2001), 8(16), 1248-1254
CODEN: GETHEC; ISSN: 0969-7128
PB Nature Publishing Group
DT Journal
LA English
CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 1, 10, 13
AB Adeno-associated virus (AAV) vectors package single-stranded genomes and require host-cell synthesis of the complementary strand for transduction. However, when the genome is half wild-type size, AAV can package either two copies, or dimeric inverted repeat DNA mols. Dimeric, or self-complementary mols. (scAAV) should spontaneously reanneal, alleviating the requirement for host-cell DNA synthesis. We generated and characterized scAAV vectors in order to bypass the rate-limiting step of second-strand synthesis. In vitro, scAAV vectors were five- to 140-fold more efficient transducing agents than conventional rAAV, with a 5.9:1 particle to transducing unit ratio. This efficiency is neither greatly increased by co-infection with Ad, nor inhibited by hydroxyurea, demonstrating that transduction is independent of DNA synthesis. In vivo, scAAV expressing erythropoietin resulted in rapid and higher levels of hematocrit than a conventional single-stranded vector. These novel scAAV vectors represent a biochem. intermediate in rAAV transduction and should provide new insights into the biol. of vector transduction.
ST genetic transduction adeno assocd virus vector dsDNA self complementary; erythropoietin recombinant scAAV vector transduction mouse liver
IT DNA
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(double-stranded; self-complementary recombinant adeno-associated virus (scAAV) vectors promote efficient transduction independently of DNA synthesis)
IT Proteins
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(green fluorescent, transgene for; self-complementary recombinant adeno-associated virus (scAAV) vectors promote efficient transduction independently of DNA synthesis)
IT Adeno-associated virus
Transformation, genetic
Viral vectors
(self-complementary recombinant adeno-associated virus (scAAV) vectors promote efficient transduction independently of DNA synthesis)
IT Transgene

RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(self-complementary recombinant adeno-associated virus (scAAV) vectors promote efficient transduction independently of DNA synthesis)
IT Gene therapy
(self-complementary recombinant adeno-associated virus (scAAV) vectors promote efficient transduction independently of DNA synthesis, in vivo transduction of mouse liver tissue by scAAV with an erythropoietin transgene)
IT Liver
(toxicity, transduced; self-complementary recombinant adeno-associated virus (scAAV) vectors promote efficient transduction independently of DNA synthesis, in vivo transduction of mouse liver tissue by scAAV with an erythropoietin transgene)
IT **HeLa cell**
(transduced; self-complementary recombinant adeno-associated virus (scAAV) vectors promote efficient transduction independently of DNA synthesis)
IT Liver
Mus
(transduced; self-complementary recombinant adeno-associated virus (scAAV) vectors promote efficient transduction independently of DNA synthesis, in vivo transduction of mouse liver tissue by scAAV with an erythropoietin transgene)
IT **11096-26-7P, Erythropoietin**
RL: **BPN (Biosynthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(self-complementary recombinant adeno-associated virus (scAAV) vectors promote efficient transduction independently of DNA synthesis, in vivo transduction of mouse liver tissue by scAAV with an **erythropoietin** transgene)
RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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(32) Zolotukhin, S; Gene Therapy 1999, V6, P973 HCAPLUS

L23 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:592207 HCAPLUS
DN 135:179815
ED Entered STN: 15 Aug 2001
TI Cytostatic process increases the productivity of cultured cells

IN Bailey, James E.; Fussenegger, Martin; Renner, Wolfgang A.
PA Switz.
SO U.S., 38 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM C12P021-02
ICS C12N005-10; C12N015-85
NCL 435069200
CC 16-6 (Fermentation and Bioindustrial Chemistry)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 6274341	B1	20010814	US 1997-948381	19971009
PRAI US 1997-948381		19971009		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 6274341	ICM	C12P021-02
	ICS	C12N005-10; C12N015-85
	NCL	435069200
US 6274341	ECLA	C07K014/47; C07K014/47A1A; C07K014/47A12; C07K014/47A33; C12N015/85

AB Provided by the invention are novel methods, vectors and cells for the recombinant production of desired gene products. In particular, the invention relates to increased production of desired gene products by inducibly arresting cell proliferation. The invention also provides novel multicistronic expression vectors that are useful not only for recombinant gene expression, but also for other applications such as gene therapy, tissue engineering and metabolic engineering.

ST animal cell culture tumor suppressor protein cytostasis
IT Animal cell line
(3T3; cytostatic process increases the productivity of cultured cells)
IT Animal cell line
(BHK; cytostatic process increases the productivity of cultured cells)
IT Animal cell line
(CHO; cytostatic process increases the productivity of cultured cells)
IT Animal cell line
(COS-7; cytostatic process increases the productivity of cultured cells)
IT Animal cell line
(HEp-2; cytostatic process increases the productivity of cultured cells)
IT Animal cell line
(HL-60; cytostatic process increases the productivity of cultured cells)
IT Animal cell line
(HT-1080; cytostatic process increases the productivity of cultured cells)
IT Animal cell line
(HaCaT; cytostatic process increases the productivity of cultured cells)
IT Animal cell line
(JURKAT; cytostatic process increases the productivity of cultured cells)
IT Animal cell line
(NSO; cytostatic process increases the productivity of cultured cells)
IT Animal cell line
(PLC/PRF/5; cytostatic process increases the productivity of cultured cells)
IT Gene therapy
Genetic engineering
Genetic vectors
HeLa cell
(cytostatic process increases the productivity of cultured cells)
IT Interleukin 2
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(cytostatic process increases the productivity of cultured cells)
IT p53 (protein)

RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(cytostatic process increases the productivity of cultured cells)

IT Glycoproteins, specific or class
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(gp160; cytostatic process increases the productivity of cultured cells)

IT Proteins, specific or class
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(green fluorescent; cytostatic process increases the productivity of cultured cells)

IT Antigens
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(hepatitis B surface; cytostatic process increases the productivity of cultured cells)

IT Animal tissue culture
(mammalian; cytostatic process increases the productivity of cultured cells)

IT Antibodies
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(monoclonal; cytostatic process increases the productivity of cultured cells)

IT Proteins, specific or class
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(p21; cytostatic process increases the productivity of cultured cells)

IT Proteins, specific or class
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(p27; cytostatic process increases the productivity of cultured cells)

IT Albumins, preparation
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(serum, human; cytostatic process increases the productivity of cultured cells)

IT Proteins, specific or class
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(tumor suppressor; cytostatic process increases the productivity of cultured cells)

IT Interferons
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(α; cytostatic process increases the productivity of cultured cells)

IT Interferons
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(β; cytostatic process increases the productivity of cultured cells)

IT Interferons
RL: BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(γ; cytostatic process increases the productivity of cultured cells)

IT 9001-25-6P, Blood coagulation Factor VII 9001-27-8P, Blood coagulation Factor VIII 9001-28-9P, Blood coagulation Factor IX 9001-78-9P, Alkaline phosphatase 9002-72-6P, Somatotropin 9003-98-9P, DNase 9004-10-8P, Insulin, preparation 9007-92-5P, Glucagon, preparation 9014-42-0P, Thrombopoietin **11096-26-7P, Erythropoietin** 62229-50-9P, EGF 83869-56-1P, GMCSF 139639-23-9P, Tissue plasminogen activator 143011-72-7P, GCSF
RL: **BMF (Bioindustrial manufacture)**; **BPN (Biosynthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(cytostatic process increases the productivity of cultured cells)

IT 355077-51-9 355077-52-0 355077-53-1 355077-54-2 355077-55-3

355077-56-4 355077-57-5 355077-58-6 355077-59-7 355077-60-0
355077-61-1 355077-62-2 355077-63-3 355077-64-4 355077-65-5
355077-66-6 355077-67-7 355077-68-8 355077-69-9 355077-70-2
RL: PRP (Properties)
(unclaimed sequence; cytostatic process increases the productivity of cultured cells)

RE.CNT 95 THERE ARE 95 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L23 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2001:453231 HCAPLUS
DN 135:32805
ED Entered STN: 22 Jun 2001
TI Arginine-enriched medium composition used for mass-producing recombinant protein in animal cell culture
IN Lee, Gyun Min; Kim, Tae Kyung; Chung, Joo Young; Park, Seung Kook
PA Daewoong Pharm. Co., Ltd., S. Korea
SO PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N005-02
ICS C12N005-06
CC 16-1 (Fermentation and Bioindustrial Chemistry)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001044442	A1	20010621	WO 2000-KR1449	20001213
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	KR 2001056451	A	20010704	KR 1999-57910	19991215
PRAI	KR 1999-57910	A	19991215		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2001044442	ICM	C12N005-02
	ICS	C12N005-06

Search done by Noble Jarrell

AB The present invention relates to an arginine-enriched medium composition used for mass-producing recombinant protein in animal cell culture. Particularly, the present invention relates to the arginine-enriched medium composition containing arginine by the concentration of 160-4200 mg/L which corresponds to 2-50 folds of the previously used medium. The arginine-enriched medium composition of the present invention can be widely used for mass-producing the recombinant protein in animal cell culture by preventing the early growth inhibition of cell and increasing the viability and life span of cell. Especially, the arginine-enriched medium composition is effectively used for mass-producing human thrombopoietin (TPO), human erythropoietin (EPO), blood coagulating agent (tPA) and antibody.

ST arginine medium compn mass recombinant protein animal cell culture

IT Animal cell line
(3T3; arginine-enriched medium composition used for mass-producing recombinant protein in animal cell culture)

IT Animal cell line
(BHK; arginine-enriched medium composition used for mass-producing recombinant protein in animal cell culture)

IT Animal cell line
(CHO; arginine-enriched medium composition used for mass-producing recombinant protein in animal cell culture)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(DHFR; arginine-enriched medium composition used for mass-producing recombinant protein in animal cell culture)

IT Animal cell
Animal tissue culture
Cell proliferation
Composition
Concentration (condition)
Culture media
Embryo, animal
HeLa cell
Longevity
Rat
(arginine-enriched medium composition used for mass-producing recombinant protein in animal cell culture)

IT Antibodies
Blood-coagulation factors
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); PREP (Preparation)
(arginine-enriched medium composition used for mass-producing recombinant protein in animal cell culture)

IT Amino acids, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(arginine-enriched medium composition used for mass-producing recombinant protein in animal cell culture)

IT Proteins, specific or class
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); PREP (Preparation)
(recombinant; arginine-enriched medium composition used for mass-producing recombinant protein in animal cell culture)

IT 9014-42-0P, Thrombopoietin **11096-26-7P, Erythropoietin**
139639-23-9P, Plasminogen activator, tissue-type
RL: **BMF (Bioindustrial manufacture)**; BIOL (Biological study); **PREP (Preparation)**
(arginine-enriched medium composition used for mass-producing recombinant protein in animal cell culture)

IT 50-99-7, Glucose, biological studies 56-85-9, Glutamine, biological studies 74-79-3, Arginine, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(arginine-enriched medium composition used for mass-producing recombinant protein in animal cell culture)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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L23 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 2000:335522 HCAPLUS
DN 132:321013
ED Entered STN: 19 May 2000
TI Method for the massive culture of cells producing recombinant human erythropoietin
IN Carcagno, Carlos Miguel; Criscuolo, Marcelo; Melo, Carlos; Vidal, Juan Alejandro
PA Sterrenbeld Biotechnologie North America, Inc., USA
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA English
IC C12N005-00; C12N005-02; A01N063-00; A01N001-02
CC 16-1 (Fermentation and Bioindustrial Chemistry)
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000027997	A1	20000518	WO 1999-US26240	19991108
	W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ				
	RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	BR 9905868	A	20010123	BR 1999-5868	19990707
	MX 9910043	A	20000930	MX 1999-10043	19991101
	CA 2350122	AA	20000518	CA 1999-2350122	19991108
	EP 1127104	A1	20010829	EP 1999-958810	19991108
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002529072	T2	20020910	JP 2000-581164	19991108
PRAI	AR 1998-105611	A	19981106		
	AR 1999-100681	A	19990223		
	WO 1999-US26240	W	19991108		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000027997	IC	C12N005-00IC C12N005-02IC A01N063-00IC A01N001-02
WO 2000027997	ECLA	C07K014/505

AB The present invention relates, in general, to a method for the massive culture of recombinant mammalian cells for the production of recombinant human erythropoietin (EPO) in culture medium containing insulin. The present invention also refers to a method of producing EPO and to the EPO thus produced.
ST massive culture cell recombinant erythropoietin
IT Animal cell line
(BKS; method for massive culture of cells producing recombinant human erythropoietin)
IT Animal cell line
(CHO; method for massive culture of cells producing recombinant human erythropoietin)
IT Animal cell line
(COS; method for massive culture of cells producing recombinant human erythropoietin)
IT Animal cell line
(Namalwa; method for massive culture of cells producing recombinant human erythropoietin)
IT Animal cell
(mammalian; method for massive culture of cells producing recombinant human erythropoietin)
IT Animal tissue culture
Blood serum
Culture media

Filtration
HeLa cell
Membrane filters
Membrane filtration
(method for massive culture of cells producing recombinant human **erythropoietin**)

IT **11096-26-7P, Erythropoietin**
RL: **BMF (Bioindustrial manufacture)**; BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); **PREP (Preparation)**; PROC (Process)
(method for massive culture of cells producing recombinant human **erythropoietin**)

IT 9004-10-8, Insulin, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(method for massive culture of cells producing recombinant human erythropoietin)

RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Jixian, D; Junshi Yixue Kexueyuan Yuankan 1997, V21(4), P244

L23 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:642960 HCAPLUS
DN 125:292149
ED Entered STN: 31 Oct 1996
TI Keratinocytes as a target for gene therapy: Sustained production of erythropoietin in mice by human keratinocytes transduced with an adenoassociated virus vector
AU Descamps, Vincent; Blumenfeld, Nadia; Beuzard, Yves; Perricaudet, Michel
CS Dep. Dermatol., Hopital Bichat, Paris, Fr.
SO Archives of Dermatology (1996), 132(10), 1207-1211
CODEN: ARDEAC; ISSN: 0003-987X
PB American Medical Association
DT Journal
LA English
CC 1-1 (Pharmacology)
Section cross-reference(s): 3
AB Keratinocytes are ideal targets for somatic gene therapy. Among the viral gene transfer systems, adeno-associated virus (AAV) vectors have recently gained attention. We studied the feasibility of using adeno-associated virus-transduced human keratinocytes to provide a long-term, high-level production of a therapeutic factor after implantation in mice. Transduction of HeLa cells by an adeno-associated virus vector was ascertained by transfer of the β-galactosidase reporter gene, which was visualized by blue staining of infected cells after fixation and coloring by X-Gal (the substrate of the reaction for β-galactosidase activity). In a second step, 2 HeLa cell lines transduced with an AAV harboring the erythropoietin complementary DNA and producing high amts. of erythropoietin in vitro were isolated. After implantation in nude mice, a high-level and long-term increase in hematocrit (for the 1-mo duration of the study) was found, which was correlated to the size of the induced tumor. In conclusion, adeno-associated virus-transduced HeLa keratinocytes provide high-level, stable, and long-term production of a therapeutic protein in mice. These results must now be extended to human primary keratinocytes.
ST human keratinocyte transgene gene therapy target; adeno assocd virus vector HeLa transformation; erythropoietin therapeutic protein prodn transgene mouse
IT **HeLa cell**
(as keratinocyte; use of keratinocytes as targets for gene therapy as shown by sustained production of **erythropoietin** in mice by implanted human keratinocytes transduced using adeno-associated virus vector)
IT Virus, animal
(adeno-associated, use of keratinocytes as targets for gene therapy as shown by sustained production of erythropoietin in mice by implanted human keratinocytes transduced using adeno-associated virus vector)
IT Therapeutics
(geno-, use of keratinocytes as targets for gene therapy as shown by sustained production of erythropoietin in mice by implanted human

keratinocytes transduced using adeno-associated virus vector)

IT Skin
(keratinocyte, use of keratinocytes as targets for gene therapy as shown by sustained production of erythropoietin in mice by implanted human keratinocytes transduced using adeno-associated virus vector)

IT Gene
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(transgene, erythropoietin, expression of; use of keratinocytes as targets for gene therapy as shown by sustained production of erythropoietin in mice by implanted human keratinocytes transduced using adeno-associated virus vector)

IT 11096-26-7, Erythropoietin
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence); USES (Uses)
(use of keratinocytes as targets for gene therapy as shown by sustained production of erythropoietin in mice by implanted human keratinocytes transduced using adeno-associated virus vector)

L23 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1996:58252 HCAPLUS
DN 124:78726
ED Entered STN: 30 Jan 1996
TI DNA construct for effecting homologous recombination and uses for recombinant protein production
IN Treco, Douglas A.; Heartlein, Michael W.; Selden, Richard F.
PA Transkaryotic Therapies, Inc., USA
SO PCT Int. Appl., 147 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM C12N015-67
ICS C12N015-90; C12N015-85; C12N015-62; C12N005-06; C07K014-505; C07K014-61; A61K048-00
CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 2, 6, 7, 15
FAN.CNT 10

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9531560	A1	19951123	WO 1995-US6045	19950511
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5641670	A	19970624	US 1994-243391	19940513
	CN 1119545	A	19960403	CN 1994-107587	19940602
	AU 9525504	A1	19951205	AU 1995-25504	19950511
	AU 709058	B2	19990819		
	EP 759082	A1	19970226	EP 1995-919831	19950511
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
	BR 9507874	A	19970819	BR 1995-7874	19950511
	JP 10500570	T2	19980120	JP 1995-529826	19950511
	FI 9604536	A	19970109	FI 1996-4536	19961112
	NO 9604802	A	19970109	NO 1996-4802	19961112
PRAI	US 1994-243391	A	19940513		
	US 1991-787840	B2	19911105		
	US 1991-789188	B2	19911105		
	US 1992-911533	B2	19920710		
	US 1992-985586	B2	19921203		
	WO 1995-US6045	A	19950511		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9531560	ICM	C12N015-67
	ICS	C12N015-90; C12N015-85; C12N015-62; C12N005-06; C07K014-505; C07K014-61; A61K048-00

WO 9531560 ECLA C07K014/505; C12N015/85; C12N015/90B4; C12N015/67
US 5641670 ECLA A61K048/00; C07K014/505; C07K014/605; C07K014/61; C12N015/67; C12N015/85; C12N015/90B4

AB The invention relates to constructs comprising: a) a targeting sequence; b) a regulatory sequence; c) an exon; and d) an unpaired splice-donor site. The invention further relates to a method of producing protein in vitro or in vivo comprising the homologous recombination of a construct as described above within the cell. The homologously recombinant cell is then maintained under conditions which will permit transcription and transition, resulting in protein expression. The present invention further relates to homologously recombinant cells, including primary, secondary, or immortalized vertebrate cells, methods of making the cells, methods of homologous recombination to produce fusion genes, methods of altering gene expression in the cells, and methods of making a protein in a cell employing the constructs of the invention.

ST recombinant protein prodn homologous recombination DNA; cytokine recombinant prodn homologous recombination; enzyme recombinant prodn homologous recombination; hormone recombinant prodn homologous recombination

IT Animal cell line
(2780AD ovarian carcinoma; DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal
Eukaryote
Fungi
Genetic marker
HeLa cell
Immunomodulators
Mouse
Plant
(DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Antibodies
Antigens
Blood-coagulation factors
Enzymes
Globins
Hormones
Immunoglobulins
Lymphokines and Cytokines
Receptors
Ribonucleic acid formation factors
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Actins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Collagens, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Gene, microbial
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Genetic element
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal cell line
(WI-38VA13 subline 2R4; DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal growth regulators
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)

(bone growth factor-2; DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal growth regulators
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(bone growth factor-7; DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Plasmid and Episome
(pREP018; DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Codon
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(AUG, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal cell line
(Bowes, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Antigens
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(CD4, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal cell line
(Daudi, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal cell line
(HL-60, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal cell line
(HT-1080, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Metallothioneins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(I, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal cell line
(JURKAT, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal cell line
(K562, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal cell line
(KB, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal cell line
(MCF-7, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal cell line
(Molt 4, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal cell line
(Namalwa, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal cell line
(RPMI 8226, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal cell line
(Raji, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Genetic element
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(SAR (scaffold attachment region), DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Animal cell line
(U937, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Lipoproteins
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP

(Preparation)
(apo-, A-I, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Lipoproteins
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(apo-, E, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Genetic element
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(cap site, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Antibodies
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(catalytic, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Virus, animal
(cytomegalo-, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Protein formation elongation factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(eEF-1α, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Genetic element
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(enhancer element, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Recombination, genetic
(homologous, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Lymphokines and Cytokines
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(interleukin 1, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Lymphokines and Cytokines
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(interleukin 11, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Lymphokines and Cytokines
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(interleukin 12, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Lymphokine and cytokine receptors
Lymphokines and Cytokines
Receptors
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(interleukin 2, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Lymphokines and Cytokines
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(interleukin 3, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Lymphokines and Cytokines
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(interleukin 6, DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Lipoprotein receptors
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(low-d., DNA construct for effecting homologous recombination and uses for recombinant protein production)

IT Receptors
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(low-d. lipoprotein, DNA construct for effecting homologous recombination and uses for recombinant protein production)
IT Genetic element
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(promoter, DNA construct for effecting homologous recombination and uses for recombinant protein production)
IT Proteins, specific or class
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(regulatory, DNA construct for effecting homologous recombination and uses for recombinant protein production)
IT Proteins, specific or class
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(structural, DNA construct for effecting homologous recombination and uses for recombinant protein production)
IT Proteins, specific or class
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(transporting, DNA construct for effecting homologous recombination and uses for recombinant protein production)
IT Lymphokines and Cytokines
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(tumor necrosis factor, DNA construct for effecting homologous recombination and uses for recombinant protein production)
IT Animal
(vertebrate, DNA construct for effecting homologous recombination and uses for recombinant protein production)
IT Interferons
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(α, DNA construct for effecting homologous recombination and uses for recombinant protein production)
IT Interferons
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(β, DNA construct for effecting homologous recombination and uses for recombinant protein production)
IT Animal growth regulators
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(β-transforming growth factors, DNA construct for effecting homologous recombination and uses for recombinant protein production)
IT Interferons
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(γ, DNA construct for effecting homologous recombination and uses for recombinant protein production)
IT 9000-94-6P, Antithrombin III 9001-24-5P, Blood coagulation factor V 9001-25-6P, Blood coagulation factor Vii 9001-28-9P, Blood coagulation factor ix 9001-29-0P, Blood coagulation factor x 9002-64-6P, Parathyroid hormone 9002-72-6P, Somatotropin 9003-98-9P, Dnase 9004-10-8P, Insulin, preparation 9007-12-9P, Calcitonin 9007-92-5P, Glucagon, preparation 9013-56-3P, Blood coagulation factor xiii 9025-35-8P, α-Galactosidase 9036-22-0P, Tyrosine hydroxylase 9039-53-6P, Urokinase 9041-92-3P, α1-Antitrypsin 9054-89-1P, Superoxide dismutase 9061-61-4P, Nerve growth factor **11096-26-7P**, **Erythropoietin** 37228-64-1P, Glucocerebrosidase 61912-98-9P, Insulin-like growth factor 62683-29-8P, Csf 81627-83-0P, m-Csf 113189-02-9P, Blood coagulation factor Viii 118549-37-4P, Insulinotropin 139639-23-9P, Tissue plasminogen activator 141436-78-4P, Protein kinase c 143011-72-7P, g-CSF
RL: **BPN (Biosynthetic preparation)**; BIOL (Biological study); **PREP (Preparation)**
(DNA construct for effecting homologous recombination and uses for

recombinant protein production)
IT 9028-35-7, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(DNA construct for effecting homologous recombination and uses for recombinant protein production)
IT 9002-68-0P, Follicle stimulating hormone 9002-71-5P, TSH
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(β; DNA construct for effecting homologous recombination and uses for recombinant protein production)

L23 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1992:524676 HCAPLUS
DN 117:124676
ED Entered STN: 04 Oct 1992
TI Purification and characterization of recombinant human erythropoietin expressed in human cervix carcinoma HeLa cells
AU Ohashi, Hideya; Miyata, Miki; Ishii, Yasuyuki; Takeuchi, Makoto; Takasago, Akemi; Suzuki, Takamoto; Sudo, Tadashi
CS Pharm. Lab., Kirin Brew. Co., Ltd., Gunma, 371, Japan
SO Trends Anim. Cell Cult. Technol., Proc. Annu. Meet. Jpn. Assoc. Anim. Cell Technol., 2nd (1990), Meeting Date 1989, 115-20. Editor(s): Murakami, Hiroki. Publisher: Kodansha, Tokyo, Japan.
CODEN: 58ADAS
DT Conference
LA English
CC 2-1 (Mammalian Hormones)
AB The establishment of a transfected HeLa cell line producing recombinant human erythropoietin (rHuEPO) and some characteristics of rHuEPO derived from HeLa cells are described. HeLa cells were found to be suitable as a host cell line for the production of recombinant glycoproteins.
ST erythropoietin recombinant HeLa cell
IT **HeLa cell**
(**erythropoietin** of human expressed in, purification and characterization of)
IT **11096-26-7P, Erythropoietin**
RL: **PREP (Preparation)**
(recombinant human, purification and characterization of, in HeLa cells)

=> b medl
FILE 'MEDLINE' ENTERED AT 14:07:31 ON 12 APR 2005

FILE LAST UPDATED: 9 APR 2005 (20050409/UP). FILE COVERS 1950 TO DATE.

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http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all l29 tot

L29 ANSWER 1 OF 8 MEDLINE on STN
AN **2000076248** MEDLINE
DN PubMed ID: 10607693
TI DNA methylation represses the expression of the human erythropoietin gene by two different mechanisms.
CM Erratum in: Blood 2000 Feb 15;95(4):1137
AU Yin H; Blanchard K L

CS Feist-Weiller Cancer Center, Department of Medicine, Louisiana State University Medical Center, Shreveport, LA 71103, USA.
NC DK-46967 (NIDDK)
SO Blood, (2000 Jan 1) 95 (1) 111-9.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200001
ED Entered STN: 20000209
Last Updated on STN: 20000824
Entered Medline: 20000131
AB The human erythropoietin gene is expressed predominantly in the kidney and liver in response to hypoxia. Although the signaling cascade for hypoxia is present in many different cell types, the expression of erythropoietin is restricted to only a few tissues. The authors show that the promoter and 5'-untranslated region (5'-UTR) of the erythropoietin gene comprise a CpG island and that methylation of the CpG island correlates inversely with expression. Methylation represses the expression of the erythropoietin gene in 2 ways: high-density methylation of the 5'-UTR recruits a methyl-CpG binding protein to the promoter, and methylation of CpGs in the proximal promoter blocks the association of nuclear proteins. (Blood. 2000;95:111-119)
CT 5' Untranslated Regions: CH, chemistry
5' Untranslated Regions: GE, genetics
Base Sequence
DNA: CH, chemistry
DNA: GE, genetics
*DNA Methylation
Dinucleoside Phosphates: AN, analysis
Erythropoietin: BI, biosynthesis
*Erythropoietin: GE, genetics
*Gene Expression Regulation
Hela Cells
Humans
Luciferases: AN, analysis
Luciferases: GE, genetics
Nucleic Acid Conformation
Polymerase Chain Reaction
Promoter Regions (Genetics): GE, genetics
Recombinant Proteins: BI, biosynthesis
Research Support, U.S. Gov't, P.H.S.
Restriction Mapping
Transfection
Tumor Cells, Cultured
RN 11096-26-7 (Erythropoietin); 2382-65-2 (cytidylyl-3'-5'-guanosine); 9007-49-2 (DNA)
CN 0 (5' Untranslated Regions); 0 (Dinucleoside Phosphates); 0 (Recombinant Proteins); EC 1.13.12.- (Luciferases)

L29 ANSWER 2 OF 8 MEDLINE on STN
AN **1998316650** MEDLINE
DN PubMed ID: 9654078
TI Oxygen-regulated erythropoietin gene expression is dependent on a CpG methylation-free hypoxia-inducible factor-1 DNA-binding site.
AU Wenger R H; Kvietikova I; Rolfs A; Camenisch G; Gassmann M
CS Institute of Physiology, University of Zurich-Irchel, Zurich, Switzerland.. labbauer@physiol.unizh.ch
SO European journal of biochemistry / FEBS, (1998 May 1) 253 (3) 771-7.
Journal code: 0107600. ISSN: 0014-2956.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199807
ED Entered STN: 19980811
Last Updated on STN: 19980811
Entered Medline: 19980729
AB The hypoxia-inducible factor-1 (HIF-1) is a transcriptional activator

involved in the expression of oxygen-regulated genes such as that for erythropoietin. Following exposure to low oxygen partial pressure (hypoxia), HIF-1 binds to an hypoxia-response element located 3' to the erythropoietin gene and confers activation of erythropoietin expression. The conserved core HIF-1 binding site (HBS) of the erythropoietin 3' enhancer (CGTG) contains a CpG dinucleotide known to be a potential target of cytosine methylation. We found that methylation of the HBS abolishes HIF-1 DNA binding as well as hypoxic reporter gene activation, suggesting that a methylation-free HBS is mandatory for HIF-1 function. The in vivo methylation pattern of the erythropoietin 3' HBS in various human cell lines and mouse organs was assessed by genomic Southern blotting using a methylation-sensitive restriction enzyme. Whereas this site was essentially methylation-free in the erythropoietin-producing cell line Hep3B, a direct correlation between erythropoietin protein expression and the degree of erythropoietin 3' HBS methylation was found in different HepG2 sublines. However, the finding that this site is partially methylation-free in human cell lines and mouse tissues that do not express erythropoietin suggests that there might be a general selective pressure to keep this site methylation-free, independent of erythropoietin expression.

CT Animals
Binding Sites
Carcinoma, Hepatocellular
*Cell Hypoxia
Cell Nucleus: ME, metabolism
DNA Methylation
*DNA-Binding Proteins: ME, metabolism
*Dinucleoside Phosphates: ME, metabolism
***Erythropoietin: BI, biosynthesis**
*Gene Expression Regulation
Gene Expression Regulation, Neoplastic
Genes, Reporter
Hela Cells
Humans
Kidney: EM, embryology
Kidney: GD, growth & development
Kidney: ME, metabolism
L Cells (Cell Line)
Leukemia
Liver: EM, embryology
Liver: GD, growth & development
Liver: ME, metabolism
Liver Neoplasms
Luciferases: BI, biosynthesis
Mice
Neuroblastoma
*Nuclear Proteins: ME, metabolism
Organ Specificity
Recombinant Fusion Proteins: BI, biosynthesis
Research Support, Non-U.S. Gov't
Transcription Factors: ME, metabolism
Transfection
Tumor Cells, Cultured

RN 11096-26-7 (Erythropoietin); 2382-65-2 (cytidylyl-3'-5'-guanosine)
CN 0 (DNA-Binding Proteins); 0 (Dinucleoside Phosphates); 0 (Nuclear Proteins); 0 (Recombinant Fusion Proteins); 0 (Transcription Factors); 0 (hypoxia-inducible factor 1); 0 (hypoxia-inducible factor 1, alpha subunit); EC 1.13.12.- (Luciferases)

L29 ANSWER 3 OF 8 MEDLINE on STN
AN **97012216** MEDLINE
DN PubMed ID: 8859032
TI Keratinocytes as a target for gene therapy. Sustained production of erythropoietin in mice by human keratinocytes transduced with an adenoassociated virus vector.
AU Descamps V; Blumenfeld N; Beuzard Y; Perricaudet M
CS Department of Dermatology, Hopital Bichat, Paris, France.
SO Archives of dermatology, (1996 Oct) 132 (10) 1207-11.
Journal code: 0372433. ISSN: 0003-987X.
CY United States

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199611
ED Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961113
AB BACKGROUND AND DESIGN: Keratinocytes are ideal targets for somatic gene therapy. Among the viral gene transfer systems, adenoassociated virus vectors have recently gained attention. We studied the feasibility of using adenoassociated virus-transduced human keratinocytes to provide a long-term, high-level production of a therapeutic factor after implantation in mice. RESULTS: Transduction of HeLa cells by an adenoassociated virus vector was ascertained by transfer of the beta-galactosidase reporter gene, which was visualized by the blue staining of infected cells after fixation and coloring by X-Gal (the substrate of the reaction for beta-galactosidase activity). In a second step, 2 HeLa cell lines transduced with an AAV harboring the erythropoietin complementary DNA and producing high amounts of erythropoietin in vitro were isolated. After implantation in nude mice, a high-level and long-term increase in hematocrit (for the 1-month duration of the study) was found, which was correlated to the size of the induced tumor. CONCLUSIONS: Adenoassociated virus-transduced HeLa keratinocytes provide high-level, stable, and long-term production of a therapeutic protein in mice. These results must now be extended to human primary keratinocytes.
CT Animals
*Dependovirus
***Erythropoietin: BI, biosynthesis**
*Gene Therapy
*Genetic Vectors
Hela Cells
Humans
*Keratinocytes: ME, metabolism
Mice
Mice, Nude
Research Support, Non-U.S. Gov't
Transduction, Genetic
RN 11096-26-7 (Erythropoietin)
CN 0 (Genetic Vectors)

L29 ANSWER 4 OF 8 MEDLINE on STN
AN **95403327** MEDLINE
DN PubMed ID: 7673128
TI Hypoxic regulation of lactate dehydrogenase A. Interaction between hypoxia-inducible factor 1 and cAMP response elements.
AU Firth J D; Ebert B L; Ratcliffe P J
CS Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, United Kingdom.
SO Journal of biological chemistry, (1995 Sep 8) 270 (36) 21021-7.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199510
ED Entered STN: 19951026
Last Updated on STN: 19970203
Entered Medline: 19951018
AB The oxygen-regulated control system responsible for the induction of erythropoietin (Epo) by hypoxia is present in most (if not all) cells and operates on other genes, including those involved in energy metabolism. To understand the organization of cis-acting sequences that are responsible for oxygen-regulated gene expression, we have studied the 5' flanking region of the mouse gene encoding the hypoxically inducible enzyme lactate dehydrogenase A (LDH). Deletional and mutational analysis of the function of mouse LDH-reporter fusion gene constructs in transient transfection assays defined three domains, between -41 and -84 base pairs upstream of the transcription initiation site, which were crucial for oxygen-regulated expression. The most important of these, although not

capable of driving hypoxic induction in isolation, had the consensus of a hypoxia-inducible factor 1 (HIF-1) site, and cross-competed for the binding of HIF-1 with functionally active Epo and phosphoglycerate kinase-1 sequences. The second domain was positioned close to the HIF-1 site, in an analogous position to one of the critical regions in the Epo 3' hypoxic enhancer. The third domain had the motif of a cAMP response element (CRE). Activation of cAMP by forskolin had no effect on the level of LDH mRNA in normoxia, but produced a magnified response to hypoxia that was dependent upon the integrity of the CRE, indicating an interaction between inducible factors binding the HIF-1 and CRE sites.

CT Animals
Base Sequence
Cell Hypoxia
DNA Mutational Analysis
*DNA-Binding Proteins: ME, metabolism.
Erythropoietin: BI, biosynthesis
Erythropoietin: GE, genetics
Forskolin: PD, pharmacology
Gene Expression Regulation, Enzymologic: DE, drug effects
Hela Cells
Humans
L-Lactate Dehydrogenase: GE, genetics
*L-Lactate Dehydrogenase: ME, metabolism
Mice
Molecular Sequence Data
*Nuclear Proteins: ME, metabolism
*Oxygen: ME, metabolism
*Regulatory Sequences, Nucleic Acid
Research Support, Non-U.S. Gov't
Sequence Deletion
*Transcription Factors
RN 11096-26-7 (Erythropoietin); 66428-89-5 (Forskolin); 7782-44-7 (Oxygen)
CN 0 (DNA-Binding Proteins); 0 (Nuclear Proteins); 0 (Transcription Factors); 0 (hypoxia-inducible factor 1); 0 (hypoxia-inducible factor 1, alpha subunit); EC 1.1.1.27 (L-Lactate Dehydrogenase)
GEN LDH-A

L29 ANSWER 5 OF 8 MEDLINE on STN
AN **95198733** MEDLINE
DN PubMed ID: 7891708
TI The orphan receptor hepatic nuclear factor 4 functions as a transcriptional activator for tissue-specific and hypoxia-specific erythropoietin gene expression and is antagonized by EAR3/COUP-TF1.
AU Galson D L; Tsuchiya T; Tendler D S; Huang L E; Ren Y; Ogura T; Bunn H F
CS Department of Medicine, Brigham & Women's Hospital, Boston, Massachusetts 02115.
NC RO1-DK41234 (NIDDK)
RO1-GM26444 (NIGMS)
SO Molecular and cellular biology, (1995 Apr) 15 (4) 2135-44.
Journal code: 8109087. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-L16588
EM 199504
ED Entered STN: 19950427
Last Updated on STN: 19990129
Entered Medline: 19950420
AB The erythropoietin (Epo) gene is regulated by hypoxia-inducible cis-acting elements in the promoter and in a 3' enhancer, both of which contain consensus hexanucleotide hormone receptor response elements which are important for function. A group of 11 orphan nuclear receptors, transcribed and translated in vitro, were screened by the electrophoretic mobility shift assay. Of these, hepatic nuclear factor 4 (HNF-4), TR2-11, ROR alpha 1, and EAR3/COUP-TF1 bound specifically to the response elements in the Epo promoter and enhancer and, except for ROR alpha 1, formed DNA-protein complexes that had mobilities similar to those observed in nuclear extracts of the Epo-producing cell line Hep3B. Moreover, both anti-HNF-4 and anti-COUP antibodies were able to supershift complexes in

Hep3B nuclear extracts. Like Epo, HNF-4 is expressed in kidney, liver, and Hep3B cells but not in HeLa cells. Transfection of a plasmid expressing HNF-4 into HeLa cells enabled an eightfold increase in the hypoxic induction of a luciferase reporter construct which contains the minimal Epo enhancer and Epo promoter, provided that the nuclear hormone receptor consensus DNA elements in both the promoter and the enhancer were intact. The augmentation by HNF-4 in HeLa cells could be abrogated by cotransfection with HNF-4 delta C, which retains the DNA binding domain of HNF-4 but lacks the C-terminal activation domain. Moreover, the hypoxia-induced expression of the endogenous Epo gene was significantly inhibited in Hep3B cells stably transfected with HNF-4 delta C. On the other hand, cotransfection of EAR3/COUP-TF1 and the Epo reporter either with HNF-4 into HeLa cells or alone into Hep3B cells suppressed the hypoxia induction of the Epo reporter. These electrophoretic mobility shift assay and functional experiments indicate that HNF-4 plays a critical positive role in the tissue-specific and hypoxia-inducible expression of the Epo gene, whereas the COUP family has a negative modulatory role.

CT Anaerobiosis
Base Sequence
Cell Nucleus: CH, chemistry
Cells, Cultured
*DNA-Binding Proteins: ME, metabolism
Erythropoietin: BI, biosynthesis
*Erythropoietin: GE, genetics
*Gene Expression Regulation
Genes, Reporter
Genetic Vectors
Hela Cells
Humans
Molecular Sequence Data
*Phosphoproteins
Promoter Regions (Genetics): GE, genetics
Protein Binding
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
*Transcription Factors: ME, metabolism
*Transcription, Genetic
Transfection

RN 11096-26-7 (Erythropoietin); 135845-90-8 (hepatocyte nuclear factor 4)
CN 0 (DNA-Binding Proteins); 0 (Genetic Vectors); 0 (Phosphoproteins); 0 (TCFL4 protein, human); 0 (Transcription Factors); 0 (chicken ovalbumin upstream promoter-transcription factor I)

L29 ANSWER 6 OF 8 MEDLINE on STN
AN **94294408** MEDLINE
DN PubMed ID: 8022811
TI Oxygen-regulated control elements in the phosphoglycerate kinase 1 and lactate dehydrogenase A genes: similarities with the erythropoietin 3' enhancer.
AU Firth J D; Ebert B L; Pugh C W; Ratcliffe P J
CS Erythropoietin Group, Institute of Molecular Medicine, John Radcliffe Hospital, Headington, Oxford, England.
SO Proceedings of the National Academy of Sciences of the United States of America, (1994 Jul 5) 91 (14) 6496-500.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199408
ED Entered STN: 19940815
Last Updated on STN: 19980206
Entered Medline: 19940801
AB Production of the glycoprotein hormone erythropoietin (Epo) in response to hypoxic stimuli is almost entirely restricted to particular cells within liver and kidney, yet the transcriptional enhancer lying 3' to the Epo gene shows activity inducible by hypoxia after transfection into a wide variety of cultured cells. The implication of this finding is that many cells which do not produce Epo contain a similar, if not identical,

oxygen-regulated control system, suggesting that the same system is involved in the regulation of other genes. We report that the human phosphoglycerate kinase 1 and mouse lactate dehydrogenase A genes are induced by hypoxia with characteristics which resemble induction of the Epo gene. In each case expression is induced by cobalt, but not by cyanide, and hypoxic induction is blocked by the protein-synthesis inhibitor cycloheximide. We show that the relevant cis-acting control sequences are located in the 5' flanking regions of the two genes, and we define an 18-bp element in the 5' flanking sequence of the phosphoglycerate kinase 1 gene which is both necessary and sufficient for the hypoxic response, and which has sequence and protein-binding similarities to the hypoxia-inducible factor 1 binding site within the Epo 3' enhancer.

CT Check Tags: Comparative Study
Animals
Base Sequence
Carcinoma, Hepatocellular
Cell Hypoxia
Cell Line
Cloning, Molecular
Cobalt: PD, pharmacology
Cyanides: PD, pharmacology
Cycloheximide: PD, pharmacology
*Enhancer Elements (Genetics)
Erythropoietin: BI, biosynthesis
*Erythropoietin: GE, genetics
Gene Expression Regulation, Enzymologic: DE, drug effects
*Gene Expression Regulation, Enzymologic: PH, physiology
Hela Cells
Humans
Isoenzymes: BI, biosynthesis
Isoenzymes: GE, genetics
L Cells (Cell Line)
L-Lactate Dehydrogenase: BI, biosynthesis
*L-Lactate Dehydrogenase: GE, genetics
Liver Neoplasms
Mice
Molecular Sequence Data
*Oxygen: PD, pharmacology
Phosphoglycerate Kinase: BI, biosynthesis
*Phosphoglycerate Kinase: GE, genetics
Promoter Regions (Genetics)
Research Support, Non-U.S. Gov't
Sequence Deletion
Sequence Homology, Nucleic Acid
TATA Box
Transfection
Tumor Cells, Cultured

RN 11096-26-7 (Erythropoietin); 66-81-9 (Cycloheximide); 7440-48-4 (Cobalt); 7646-79-9 (cobaltous chloride); 7782-44-7 (Oxygen)

CN 0 (Cyanides); 0 (Isoenzymes); EC 1.1.1.27 (L-Lactate Dehydrogenase); EC 2.7.2.3 (Phosphoglycerate Kinase)

L29 ANSWER 7 OF 8 MEDLINE on STN
AN **94241589** MEDLINE
DN PubMed ID: 8185223
TI Study of regulatory elements involved in erythropoietin gene expression using minigene constructs.
AU Ramirez S; Beck I; Salceda S; Caro J
CS Cardeza Foundation for Hematologic Research, Jefferson Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania 19107.
SO Annals of the New York Academy of Sciences, (1994 Apr 15) 718 13-8; discussion 18-20. Ref: 20
Journal code: 7506858. ISSN: 0077-8923.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals

EM 199406
ED Entered STN: 19940621
Last Updated on STN: 19970203
Entered Medline: 19940614
CT Animals
Cell Hypoxia
Cell Line
***Erythropoietin: BI, biosynthesis**
Erythropoietin: GE, genetics
*Gene Expression
Gene Expression Regulation
Hela Cells
Humans
Nuclear Proteins: ME, metabolism
*Regulatory Sequences, Nucleic Acid
Restriction Mapping
Transcription, Genetic
Transfection
RN 11096-26-7 (Erythropoietin)
CN 0 (Nuclear Proteins)

L29 ANSWER 8 OF 8 MEDLINE on STN
AN **93248278** MEDLINE
DN PubMed ID: 8387214
TI General involvement of hypoxia-inducible factor 1 in transcriptional response to hypoxia.
AU Wang G L; Semenza G L
CS Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD 21205.
SO Proceedings of the National Academy of Sciences of the United States of America, (1993 May 1) 90 (9) 4304-8.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199306
ED Entered STN: 19930618
Last Updated on STN: 19980206
Entered Medline: 19930601
AB Transcription of the human erythropoietin (EPO) gene is activated in Hep3B cells exposed to hypoxia. Hypoxia-inducible factor 1 (HIF-1) is a nuclear factor whose DNA binding activity is induced by hypoxia in Hep3B cells, and HIF-1 binds at a site in the EPO gene enhancer that is required for hypoxic activation of transcription. In this paper, we demonstrate that HIF-1 DNA binding activity is also induced by hypoxia in a variety of mammalian cell lines in which the EPO gene is not transcribed. The composition of the HIF-1 DNA binding complex and its isolated DNA binding subunit and the mechanism of HIF-1 activation appear to be similar or identical in EPO-producing and non-EPO-producing cells. Transcription of reporter genes containing the EPO gene enhancer is induced by hypoxia in non-EPO-producing cells and mutations that eliminate HIF-1 binding eliminate inducibility. These results provide evidence that HIF-1 and its recognition sequence are common components of a general mammalian cellular response to hypoxia.
CT Animals
Base Sequence
Binding Sites
CHO Cells
Carcinoma, Hepatocellular
Cell Hypoxia
Cell Nucleus: ME, metabolism
Cell Nucleus: RE, radiation effects
Chloramphenicol O-Acetyltransferase: GE, genetics
Chloramphenicol O-Acetyltransferase: ME, metabolism
DNA-Binding Proteins: IP, isolation & purification
*DNA-Binding Proteins: ME, metabolism
*Enhancer Elements (Genetics)
Erythropoietin: BI, biosynthesis
*Erythropoietin: GE, genetics

*Gene Expression Regulation, Neoplastic
Hamsters
Hela Cells
Humans
Liver Neoplasms
Macromolecular Substances
Molecular Sequence Data
Nuclear Proteins: IP, isolation & purification
*Nuclear Proteins: ME, metabolism
Oligonucleotide Probes
Recombinant Fusion Proteins: ME, metabolism
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.
*Transcription Factors
*Transcription, Genetic
Transfection
Tumor Cells, Cultured
Ultraviolet Rays
beta-Galactosidase: GE, genetics
beta-Galactosidase: ME, metabolism
RN 11096-26-7 (Erythropoietin)
CN 0 (DNA-Binding Proteins); 0 (Macromolecular Substances); 0 (Nuclear Proteins); 0 (Oligonucleotide Probes); 0 (Recombinant Fusion Proteins); 0 (Transcription Factors); 0 (hypoxia-inducible factor 1); 0 (hypoxia-inducible factor 1, alpha subunit); EC 2.3.1.28 (Chloramphenicol O-Acetyltransferase); EC 3.2.1.23 (beta-Galactosidase)
GEN EPO

=> b home
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=>

=> d his

(FILE 'HOME' ENTERED AT 13:11:39 ON 12 APR 2005)

FILE 'HCAPLUS' ENTERED AT 13:14:28 ON 12 APR 2005
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E DE1998-98113415/AP,PRN
E DE1998-19813415/AP,PRN
E DE97-19753681/AP,PRN
L1 2 DE97-19753681/AP,PRN
E DE98-98113415/AP,PRN
E DE98-19813415/AP,PRN
L2 1 WO98-EP7876#/AP,PRN
L3 2 L1-2

FILE 'REGISTRY' ENTERED AT 13:18:00 ON 12 APR 2005

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L4 TRA L3 1- RN : 14 TERMS

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L5 14 SEA L4

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L6 4 (WO98-EP7876# OR DE97-19753681#)/AP,PRN
E DE97-98113415/AP,PRN
E DE97-19813415/AP,PRN

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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 12 Apr 2005 VOL 142 ISS 16
FILE LAST UPDATED: 11 Apr 2005 (20050411/ED)

This file contains CAS Registry Numbers for easy and accurate
substance identification.

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L3 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:96350 HCAPLUS
DN 130:149562
ED Entered STN: 12 Feb 1999
TI Production of erythropoietin by endogenous gene activation of human cells
IN Stern, Anne; Brandt, Michael; Honold, Konrad; Auer, Johannes; Koll, Hans
PA Boehringer Mannheim G.m.b.H., Germany
SO PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DT Patent
LA German
IC ICM C12N015-12
ICS C12N015-85; C12N015-62; C12N015-90; C12N005-10; C07K014-505;
A61K038-18
CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 16

FAN. CNT 2

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PI	WO 9905268	A1	19990204	WO 1998-EP4590	19980722 <—
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	US 6548296	B1	20030415	US 1998-113692	19980710 <—
	CA 2298015	AA	19990204	CA 1998-2298015	19980722 <—
	AU 9889786	A1	19990216	AU 1998-89786	19980722 <—
	AU 754619	B2	20021121		
	ZA 9806515	A	20000124	ZA 1998-6515	19980722
	ZA 9806516	A	20000124	ZA 1998-6516	19980722
	EP 986644	A1	20000322	EP 1998-941401	19980722 <—
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
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	TR 200000175	T2	20010122	TR 2000-200000175	19980722 <—
	JP 2001511343	T2	20010814	JP 2000-504243	19980722 <—
	TW 574372	B	20040201	TW 1998-87116028	19980924 <—
	WO 9928455	A1	19990610	WO 1998-EP7819	19981202 <—
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
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	ZA 9811004	A	20000602	ZA 1998-11004	19981202 <—
	EP 1036179	A1	20000920	EP 1998-965223	19981202 <—
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	JP 2001525342	T2	20011211	JP 2000-523332	19981202 <—
	JP 3394240	B2	20030407		
	JP 2003180392	A2	20030702	JP 2002-321415	19981202 <—
	CA 2309810	AA	19990610	CA 1998-2309810	19981203 <—
	WO 9928346	A1	19990610	WO 1998-EP7876	19981203 <—
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	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9921581	A1	19990616	AU 1999-21581	19981203 <—
	AU 744086	B2	20020214		
	EP 1037921	A1	20000927	EP 1998-965756	19981203 <—
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
	BR 9813391	A	20001010	BR 1998-13391	19981203 <—
	TR 200001580	T2	20001221	TR 2000-200001580	19981203 <—
	JP 2001525338	T2	20011211	JP 2000-523237	19981203 <—
	JP 2003238593	A2	20030827	JP 2003-55499	19981203 <—
	US 6391633	B1	20020521	US 2000-463380	20000121 <—
	US 6555373	B1	20030429	US 2000-607277	20000630 <—
	US 6673575	B1	20040106	US 2000-555533	20000905 <—
	US 2002110913	A1	20020815	US 2001-985357	20011102 <—
	US 6544748	B2	20030408		
	AU 2002029337	A5	20020523	AU 2002-29337	20020328
	AU 776280	B2	20040902		
	US 2004203001	A1	20041014	US 2003-351397	20030127 <—
	US 2003166275	A1	20030904	US 2003-353767	20030129 <—
	JP 2004339234	A2	20041202	JP 2004-219290	20040727 <—

PRAI	EP 1997-112640	A	19970723	
	DE 1997-19753681	A	19971203	<--
	US 1998-113692	A	19980710	
	EP 1998-113415	A	19980717	
	EP 1997-121073	A	19971201	
	EP 1998-113409	A	19980717	
	WO 1998-EP4590	W	19980722	
	JP 2000-523332	A3	19981202	
	WO 1998-EP7819	W	19981202	
	JP 2000-523237	A3	19981203	
	WO 1998-EP7876	W	19981203	<--
	US 2000-463380	A1	20000121	
	US 2001-985357	A1	20011102	

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
WO 9905268	ICM	C12N015-12	
	ICS	C12N015-85; C12N015-62; C12N015-90; C12N005-10; C07K014-505; A61K038-18	
WO 9905268	ECLA	C07K014/505; C12N015/10; C12N015/62A	<--
DE 19753681	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B	<--
US 6548296	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B	<--
WO 9928455	ECLA	C07K014/505; C12P021/00B	<--
WO 9928346	ECLA	C07K014/505	<--
US 6391633	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B	<--
US 6555373	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B	<--
US 6673575	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B	<--
US 2002110913	ECLA	C07K014/505; C12N015/10; C12P021/00B; C12N015/62A	<--
US 2004203001	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B	<--
US 2003166275	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B	<--
JP 2004339234	FTERM	4B064/AG18; 4B064/CA10; 4B064/CA19; 4B064/CC24; 4B064/CD09; 4B064/CE06; 4B064/CE10; 4B064/CE12; 4B064/DA03; 4C084/AA02; 4C084/BA01; 4C084/BA09; 4C084/BA34; 4C084/CA56; 4C084/DB56; 4C084/NA05; 4C084/NA14; 4C084/ZA552; 4H045/AA10; 4H045/AA20; 4H045/AA30; 4H045/BA10; 4H045/BA53; 4H045/CA40; 4H045/DA13; 4H045/EA24; 4H045/FA74; 4H045/GA10; 4H045/GA15; 4H045/GA24; 4H045/GA25; 4H045/GA26	<--

AB The invention concerns human cells which, owing to the activation of the endogenous human erythropoietin gene, can produce erythropoietin (EPO) in sufficient quantities and degree of purity to allow human EPO to be economically produced as a pharmaceutical preparation The invention also concerns a process for producing such human EPO-producing cells, DNA-constructs for activating the endogenous EPO gene in human cells and a process for the large-scale production of EPO in human cells. A HeLa S3 cell containing erythropoietin genes fused to a cytomegalovirus immediate early promoter and enhancer was produced by homologous recombination. Optimization of the erythropoietin gene expression involved alteration of the signal sequence, shortening of the distance between the cytomegalovirus promoter and translation start site, and amplification of the gene. A recombinant cell line producing >7000 ng erythropoietin/mL/106 cells/24 h was obtained. The erythropoietin was purified by a series of chromatog. steps (affinity, hydrophobic interaction, hydroxyapatite, reverse phase HPLC) to produce erythropoietin with specific activity >100,000 units/mg.

ST erythropoietin manuf recombinant human cell cytomegalovirus immediate early promoter

IT Animal cell line
(HT-1080; production of erythropoietin by endogenous gene activation of human cells)

IT Animal cell line
(Namalwa; production of erythropoietin by endogenous gene activation of human cells)

IT HeLa cell
(S3; production of erythropoietin by endogenous gene activation of human cells)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(for erythropoietin, activation of; production of erythropoietin by

endogenous gene activation of human cells)
IT Recombination, genetic
(homologous; production of erythropoietin by endogenous gene activation of human cells)
IT Animal cell
(human; production of erythropoietin by endogenous gene activation of human cells)
IT Promoter (genetic element)
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(immediate early, of cytomegalovirus, for activation of erythropoietin gene; production of erythropoietin by endogenous gene activation of human cells)
IT Plasmid vectors
(p189; production of erythropoietin by endogenous gene activation of human cells)
IT Fermentation
(production of erythropoietin by endogenous gene activation of human cells)
IT Genetic element
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(signal sequence, modified; production of erythropoietin by endogenous gene activation of human cells)
IT Promoter (genetic element)
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(viral, for activation of erythropoietin gene; production of erythropoietin by endogenous gene activation of human cells)
IT 75432-66-5, Blue Sepharose
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(Blue Sepharose; production of erythropoietin by endogenous gene activation of human cells)
IT 9002-03-3P, Dihydrofolate reductase
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation); PROC (Process)
(gene for, as amplification gene; production of erythropoietin by endogenous gene activation of human cells)
IT 62213-36-9P, Neomycin phosphotransferase
RL: BPN (Biosynthetic preparation); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation); PROC (Process)
(gene for, as selectable marker; production of erythropoietin by endogenous gene activation of human cells)
IT 11096-26-7P, Erythropoietin
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(production of erythropoietin by endogenous gene activation of human cells)
IT 72980-05-3
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(production of erythropoietin by endogenous gene activation of human cells)
IT 220271-95-4 220271-96-5 220271-97-6 220271-98-7
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(signal peptide N-terminus; production of erythropoietin by endogenous gene activation of human cells)
RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Applied Research Systems; WO 9109955 A 1991 HCAPLUS
(2) Boehringer Mannheim Gmbh; WO 9635718 A 1996 HCAPLUS
(3) Cangene Corp; WO 9619573 A 1996 HCAPLUS
(4) Cell Genesys Inc; EP 0747485 A 1996 HCAPLUS
(5) Genetics Inst; EP 0411678 A 1991 HCAPLUS
(6) Integrated Genetics Inc; EP 0267678 A 1988 HCAPLUS
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(9) Simonsen, C; Proceedings of the National Academy of Sciences of USA 1983, V80, P2495 HCAPLUS
(10) Sumitomo Chemical Co; EP 0232034 A 1987 HCAPLUS
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(12) Transkaryotic Therapies Inc; WO 9412650 A 1994 HCAPLUS
(13) Transkaryotic Therapies Inc; WO 9531560 A 1995 HCAPLUS
(14) Transkaryotic Therapies Inc; WO 9629411 A 1996 HCAPLUS

L3 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2005 ACS on STN
AN 1999:96349 HCAPLUS
DN 130:149561
ED Entered STN: 12 Feb 1999
TI Identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines
IN Brandt, Michael; Franze, Reinhard; Pessara, Ulrich
PA Boehringer Mannheim G.m.b.H., Germany
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA German
IC ICM C12N015-12
ICS C12N015-85; C12N015-10; C07K014-505
CC 3-2 (Biochemical Genetics)
FAN. CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9905267	A1	19990204	WO 1998-EP4584	19980722	
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	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG					
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	AU 737605	B2	20010823			
	ZA 9806515	A	20000124	ZA 1998-6515	19980722	
	ZA 9806516	A	20000124	ZA 1998-6516	19980722	
	EP 1000154	A1	20000517	EP 1998-942592	19980722	
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	MX 200000677	A	20001109	MX 2000-677	20000119	
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	AU 776280	B2	20040902			
	US 2002164792	A1	20021107	US 2002-112755	20020402	
	US 6846673	B2	20050125			
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	US 1998-113692	A	19980710			
	DE 1997-19753681	A	19971203	<--		
	WO 1998-EP4584	W	19980722			
	US 2000-463339	A1	20000530			

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES	
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	ICS	C12N015-85; C12N015-10; C07K014-505	
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US 6548296	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B	<--
US 6395484	ECLA	C07K014/505; C12N015/10; C12N015/62A	
US 6555373	ECLA	C07K014/505; C12N015/10; C12N015/62A; C12P021/00B	<--

US 2002164792 ECLA C07K014/505; C12N015/10; C12N015/62A
US 2004203001 ECLA C07K014/505; C12N015/10; C12N015/62A; C12P021/00B <—

AB A process for selecting human cells for the production of human proteins by endogenous gene activation allows human proteins to be produced in economically feasible quantities and in a form suitable for producing a pharmaceutical composition The human cells should contain the gene with the desired nucleotide sequence and should undergo at least 5 population doublings within 14 days in suspension culture and serum-free medium. Ideally, the cells should also contain >2 copies of the target gene, produce the protein with the appropriate glycosylation, and be free of infectious contaminants. Also disclosed are recombinant human cell lines containing an endogenous gene operatively fused to a heterologous promoter as well as a process for producing human proteins in such cell lines. Using the above techniques, a HeLa S3 cell containing erythropoietin genes fused to a cytomegalovirus immediate early promoter and enhancer was produced. This recombinant cell line produced >7000 ng erythropoietin/mL/106 cells/24 h.

ST human cell line heterologous promoter protein manuf; erythropoietin manuf recombinant HeLa cell cytomegalovirus early promoter

IT Animal cell line
(HT-1080; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Animal cell line
(Namalwa; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT HeLa cell
(S3; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Gene, animal
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(activation of; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Promoter (genetic element)
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(heterologous; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Proteins, general, preparation
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(human; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Animal cell line
Fermentation
(identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Blood-coagulation factors
Bone morphogenetic proteins
Chemokines
Enkephalins
Hedgehog protein
Interferons
Interleukins
Neurotrophic factors
Receptors
Transforming growth factors
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Cytomegalovirus
(immediate early promoter and enhancer of; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)

IT Promoter (genetic element)
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(immediate early, of cytomegalovirus; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)
IT Plasmid vectors
(p179, for activation of erythropoietin gene; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)
IT Plasmid vectors
(p187, for activation of erythropoietin gene; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)
IT Plasmid vectors
(p189, for activation of erythropoietin gene; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)
IT Plasmid vectors
(p190, for activation of erythropoietin gene; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)
IT Plasmid vectors
(p192, for activation of erythropoietin gene; identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)
IT 9002-60-2P, ACTH, preparation 9002-72-6P, Growth hormone 9014-42-0P, Thrombopoietin 11096-26-7P, Erythropoietin 60118-07-2P, Endorphin 62683-29-8P, Colony-stimulating factor
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(identification of human cell lines for production of human proteins by endogenous gene activation and recombinant human cell lines)
RE.CNT 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
(1) Cell Genesys Inc; EP 0747485 A 1996 HCAPLUS
(2) Genetics Inst; EP 0411678 A 1991 HCAPLUS
(3) Integrated Genetics Inc; EP 0267678 A 1988 HCAPLUS
(4) Sumitomo Chemical Co; EP 0232034 A 1987 HCAPLUS
(5) Transkaryotic Therapies Inc; WO 9309222 A 1993 HCAPLUS
(6) Transkaryotic Therapies Inc; WO 9412650 A 1994 HCAPLUS
(7) Transkaryotic Therapies Inc; WO 9531560 A 1995 HCAPLUS
(8) Transkaryotic Therapies Inc; WO 9629411 A 1996 HCAPLUS

=> b reg

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STRUCTURE FILE UPDATES: 11 APR 2005 HIGHEST RN 848290-51-7
DICTIONARY FILE UPDATES: 11 APR 2005 HIGHEST RN 848290-51-7

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *

* *
****

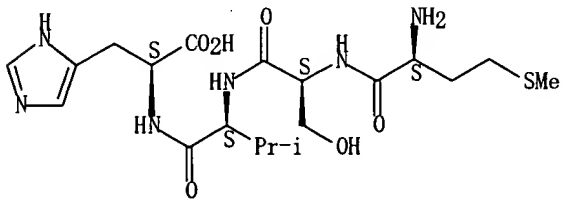
Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide l5 tot

L5 ANSWER 1 OF 14 REGISTRY COPYRIGHT 2005 ACS on STN
RN **220271-98-7** REGISTRY
ED Entered STN: 09 Mar 1999
CN L-Histidine, L-methionyl-L-seryl-L-valyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C19 H32 N6 O6 S
SR CA
LC STN Files: CA, CAPLUS

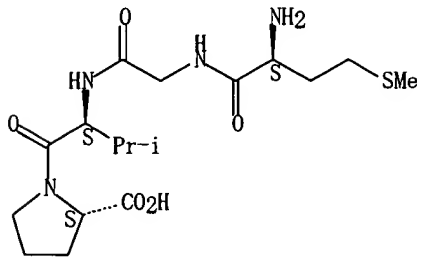
Absolute stereochemistry.



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 2 OF 14 REGISTRY COPYRIGHT 2005 ACS on STN
RN **220271-97-6** REGISTRY
ED Entered STN: 09 Mar 1999
CN L-Proline, L-methionylglycyl-L-valyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C17 H30 N4 O5 S
SR CA
LC STN Files: CA, CAPLUS

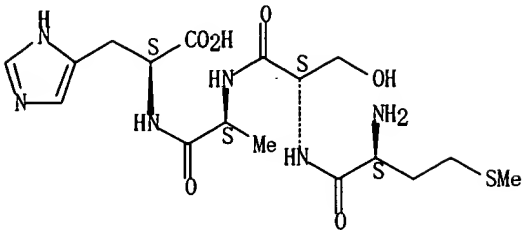
Absolute stereochemistry.



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 3 OF 14 REGISTRY COPYRIGHT 2005 ACS on STN
RN **220271-96-5** REGISTRY
ED Entered STN: 09 Mar 1999
CN L-Histidine, L-methionyl-L-seryl-L-alanyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C17 H28 N6 O6 S
SR CA
LC STN Files: CA, CAPLUS

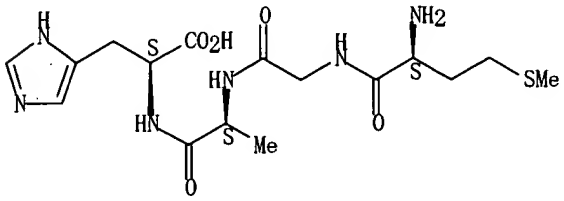
Absolute stereochemistry.



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 4 OF 14 REGISTRY COPYRIGHT 2005 ACS on STN
RN **220271-95-4** REGISTRY
ED Entered STN: 09 Mar 1999
CN L-Histidine, L-methionylglycyl-L-alanyl- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C16 H26 N6 O5 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 5 OF 14 REGISTRY COPYRIGHT 2005 ACS on STN
RN **75432-66-5** REGISTRY
ED Entered STN: 16 Nov 1984
CN Agarose, 4-[[4-[(4-amino-9,10-dihydro-9,10-dioxo-3-sulfo-1-anthracenyl)amino]-2-sulfophenyl]amino]-6-[[3(or 4)-sulfophenyl]amino]-1,3,5-triazin-2-yl ether, trisodium salt (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Agarose Blue A
CN Blue Sepharose
CN Matrex Gel Blue A
CN Sepharose blue
DR 66456-82-4, 73361-30-5, 76543-98-1, 86595-66-6
MF C29 H21 N7 O12 S3 . 3 Na . x Unspecified
LC STN Files: AGRICOLA, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CSCHEM, MEDLINE, PROMT, TOXCENTER, USPAT2, USPATFULL

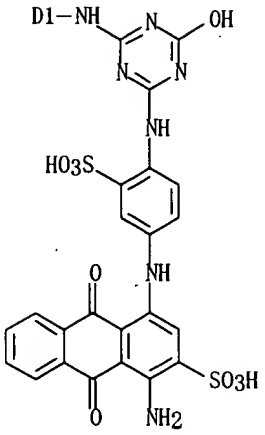
CM 1

CRN 168075-63-6
CMF C29 H21 N7 O12 S3
CCI IDS

PAGE 1-A

D1-SO3H

PAGE 2-A



CM 2

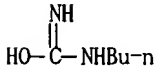
CRN 9012-36-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
104 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
104 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 6 OF 14 REGISTRY COPYRIGHT 2005 ACS on STN
RN **72980-05-3** REGISTRY
ED Entered STN: 16 Nov 1984
CN Agarose, butylcarbamimidate (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Butyl agarose
MF C5 H12 N2 O . x Unspecified
LC STN Files: BIOSIS, CA, CAPLUS, MEDLINE, TOXCENTER, USPATFULL

CM 1

CRN 171262-78-5
CMF C5 H12 N2 O



CM 2

CRN 9012-36-6
CMF Unspecified
CCI PMS, MAN

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
22 REFERENCES IN FILE CA (1907 TO DATE)
22 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 7 OF 14 REGISTRY COPYRIGHT 2005 ACS on STN
RN **62683-29-8** REGISTRY
ED Entered STN: 16 Nov 1984
CN Colony-stimulating factor (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Colony formation stimulating factor
CN Colony stimulating activity
CN Colony-stimulating glycoproteins
CN CSF
CN CSF (hormone)
CN Neutrophil alkaline phosphatase-inducing factor
MF Unspecified
CI COM, MAN
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CBNB, CEN, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, PHAR, PROMT, PROUSDDR, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
2273 REFERENCES IN FILE CA (1907 TO DATE)
58 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2274 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 8 OF 14 REGISTRY COPYRIGHT 2005 ACS on STN
RN **62213-36-9** REGISTRY
ED Entered STN: 16 Nov 1984
CN Kinase (phosphorylating), kanamycin (9CI) (CA INDEX NAME)
OTHER NAMES:
CN E.C. 2.7.1.95
CN Kanamycin kinase
CN Neomycin aminoglycoside phosphotransferase
CN Neomycin phosphotransferase
MF Unspecified
CI MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CIN, EMBASE, PROMT, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
499 REFERENCES IN FILE CA (1907 TO DATE)
13 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
500 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 9 OF 14 REGISTRY COPYRIGHT 2005 ACS on STN
RN **60118-07-2** REGISTRY
ED Entered STN: 16 Nov 1984
CN Endorphin (9CI) (CA INDEX NAME)
MF Unspecified
CI MAN
LC STN Files: ADISNEWS, AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CEN, CIN, DDFU, DRUGU, EMBASE, NAPRALERT, PHAR, PROMT, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
1122 REFERENCES IN FILE CA (1907 TO DATE)
47 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1123 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 10 OF 14 REGISTRY COPYRIGHT 2005 ACS on STN
RN **11096-26-7** REGISTRY
ED Entered STN: 16 Nov 1984
CN Erythropoietin (9CI) (CA INDEX NAME)
OTHER NAMES:

CN Ep
CN EPO
CN Epoetin
CN Epogis S
CN Hempoietine
MF Unspecified
CI COM, MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PROMT, PROUSDDR, RTECS*, TOXCENTER, USPAT2, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
9094 REFERENCES IN FILE CA (1907 TO DATE)
265 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
9106 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 11 OF 14 REGISTRY COPYRIGHT 2005 ACS on STN
RN **9014-42-0** REGISTRY
ED Entered STN: 16 Nov 1984
CN Thrombopoietin (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN c-Mpl ligand
CN Lubricin
CN Megakaryocyte colony-stimulating factor
CN Megakaryocyte growth and development factor
CN Megakaryocyte stimulating factor
CN Megapoietin
CN MGDF
CN Mpl ligand
CN PRG 4
CN Proteoglycan 4
CN Superficial zone protein
CN Thrombocytopoiesis-stimulating factor
CN Thrombocytopoietic-stimulating factor
CN Thrombocytopoietin
CN Thrombopoiesis-stimulating factor
DR 158254-29-6, 103219-27-8
MF Unspecified
CI PMS, COM, MAN
PCT Manual registration
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CBNB, CEN, CIN, EMBASE, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, PROMT, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
2080 REFERENCES IN FILE CA (1907 TO DATE)
82 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2080 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 12 OF 14 REGISTRY COPYRIGHT 2005 ACS on STN
RN **9002-72-6** REGISTRY
ED Entered STN: 16 Nov 1984
CN Somatotropin (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Adenohypophyseal growth hormone
CN Anterior hypophyseal growth hormone
CN Anterior pituitary growth hormone
CN GH
CN Growth hormone
CN Hypophyseal growth hormone
CN Phyol
CN Phyone
CN Pituitary growth hormone
CN SH

CN Somacton
CN Somatotropic hormone
CN Sotropin H
CN STH
DR 9042-17-5, 9061-43-2, 9067-08-7
MF Unspecified
CI PMS, COM, MAN
PCT Manual registration
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, AQUIRE, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
32232 REFERENCES IN FILE CA (1907 TO DATE)
615 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
32261 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 13 OF 14 REGISTRY COPYRIGHT 2005 ACS on STN
RN **9002-60-2** REGISTRY
ED Entered STN: 16 Nov 1984
CN Corticotropin (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Acethropan
CN Acortan
CN Acorto
CN ACTH
CN Acthar
CN Acthormone
CN Acton
CN Acton (hormone)
CN Actonar
CN Adrenal cortex hormone
CN Adrenocorticotrophic hormone
CN Adrenocorticotrophin
CN Adrenocorticotropic hormone
CN Adrenocorticotropin
CN Adrenocorticotropin hormone
CN Adrenomone
CN Adrenotrophin
CN Alfatrofin
CN Chorionic corticotropin
CN Cibacthen
CN Corstiline
CN Corticotrophin
CN Corticotropin-like substances
CN Cortiphyson
CN Cortrophimn
CN Cortrophin
CN Duracton
CN Dynamone
CN Exacthin
CN Humactid
CN Isactid
CN Nuvacthen
CN ProActon
CN Reacthin
CN Solacthyl
CN Tubex
DR 8049-37-4, 8049-43-2, 8049-68-1, 8049-86-3, 8049-87-4, 9006-61-5, 9040-10-2, 55127-96-3
MF Unspecified
CI PMS, COM, MAN
PCT Manual registration
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM,

CSNB, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA,
MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PROMT, RTECS*, TOXCENTER,
USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
24644 REFERENCES IN FILE CA (1907 TO DATE)
356 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
24652 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L5 ANSWER 14 OF 14 REGISTRY COPYRIGHT 2005 ACS on STN
RN **9002-03-3** REGISTRY
ED Entered STN: 16 Nov 1984
CN Dehydrogenase, tetrahydrofolate (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 7,8-Dihydrofolate reductase
CN Dihydrofolate dehydrogenase
CN Dihydrofolate reductase
CN Dihydrofolic acid reductase
CN Dihydrofolic reductase
CN Dihydropteroylglutamate reductase
CN E.C. 1.5.1.3
CN E.C. 1.5.1.4
CN Folate reductase
CN Folic acid reductase
CN Folic reductase
CN NADP-dihydrofolate reductase
CN NADPH-dihydrofolate reductase
CN Reductase, dihydrofolate
CN Tetrahydrofolate dehydrogenase
DR 9001-17-6, 9038-35-1
MF Unspecified
CI MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO,
CA, CABA, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CIN, CSCHEM,
EMBASE, IFICDB, IFIPAT, IFIUDB, PROMT, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
5483 REFERENCES IN FILE CA (1907 TO DATE)
368 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5489 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> b wpix

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FILE LAST UPDATED: 11 APR 2005 <20050411/UP>
MOST RECENT DERWENT UPDATE: 200523 <200523/DW>
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GUIDES, PLEASE VISIT:
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PLEASE CHECK:
http://thomsonderwent.com/support/dwpiref/reftools/classification/code-revision/
FOR DETAILS. <<<

=> d all l6 tot

L6 ANSWER 1 OF 4 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1999-371116 [31] WPIX
CR 1999-142925 [12]; 1999-371097 [31]
DNC C1999-109582
TI Obtaining glycolised polypeptides from eukaryotic cells.
DC B04 D16
IN EBERHARDT, H; FRANZE, R; WALLERIUS, C
PA (HOFF) ROCHE DIAGNOSTICS GMBH; (BOEF) BOEHRINGER MANNHEIM GMBH
CYC 85
PI WO 9928455 A1 19990610 (199931)* GE 33 C12N015-12
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
OA PT SD SE SZ UG ZW
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GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD
MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA
UG US UZ VN YU ZW
AU 9920518 A 19990616 (199945)
EP 1036179 A1 20000920 (200047) GE C12N015-12
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE
ZA 9811004 A 20000830 (200049)# 29 A61K000-00
JP 2001525342 W 20011211 (200204) 26 C07K014-505
JP 3394240 B2 20030407 (200327) 9 C07K014-505
JP 2003180392 A 20030702 (200352) 9 C12P021-00
US 6673575 B1 20040106 (200411) C12P021-00
ADT WO 9928455 A1 WO 1998-EP7819 19981202; AU 9920518 A AU 1999-20518 19981202; EP 1036179 A1 EP 1998-965223 19981202, WO 1998-EP7819 19981202; ZA 9811004 A ZA 1998-11004 19981202; JP 2001525342 W WO 1998-EP7819 19981202, JP 2000-523332 19981202; JP 3394240 B2 WO 1998-EP7819 19981202, JP 2000-523332 19981202; JP 2003180392 A Div ex JP 2000-523332 19981202, JP 2002-321415 19981202; US 6673575 B1 WO 1998-EP7819 19981202, US 2000-555533 20000905
FDT AU 9920518 A Based on WO 9928455; EP 1036179 A1 Based on WO 9928455; JP 2001525342 W Based on WO 9928455; JP 3394240 B2 Previous Publ. JP 200125342, Based on WO 9928455; US 6673575 B1 Based on WO 9928455
PRAI EP 1998-113409 19980717; **DE 1997-19753681 19971203**; ZA 1998-11004 19981202
IC ICM A61K000-00; C07K014-505; C12N015-12; C12P021-00
ICS C12N005-00; C12N005-06; C12N015-09; C12P021-02
ICA C12N005-10
AB WO 9928455 A UPAB: 20040213
NOVELTY - Obtaining glycolised polypeptides from eukaryotic cells, comprises adding at least two carbohydrates to the cell culture medium. The polypeptide is then isolated from the culture medium or the cells.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method as described above, where also nutrients and especially at least one essential amino acid is added together with the carbohydrates.
USE - The process is used in the production of erythropoietin.
ADVANTAGE - the controlled addition of nutrients and carbohydrates at high cell density fermentation leads to a high yield of the desired protein.
Dwg. 0/1
FS CPI
FA AB; DCN
MC CPI: B04-N02; D05-H01; D05-H13

L6 ANSWER 2 OF 4 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1999-371097 [31] WPIX
CR 1999-142926 [12]; 1999-371116 [31]
DNC C1999-109563
TI Erythropoietin composition has a highly specific activity.
DC B04 D16
IN BURG, J; HASELBECK, A; KOLLE, H; SELLINGER, K; KOLL, H

PA (HOFF) ROCHE DIAGNOSTICS GMBH
CYC 85
PI WO 9928346 A1 19990610 (199931)* GE 75 C07K014-505
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
DE 19753681 A1 19990722 (199935) A61K038-17
AU 9921581 A 19990616 (199945)
EP 1037921 A1 20000927 (200048) GE C07K014-505
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE
ZA 9811003 A 20000830 (200049)# 70 A61K000-00
BR 9813391 A 20001010 (200055) C07K014-505
CN 1280586 A 20010117 (200128) C07K014-505
KR 2001024681 A 20010326 (200161) C07K014-505
JP 2001525338 W 20011211 (200204) 67 C07K014-505
AU 744086 B 20020214 (200223) C07K014-505
JP 2003238593 A 20030827 (200365) 21 C07K014-505
KR 390325 B 20030707 (200409) C07K014-505
JP 2004339234 A 20041202 (200479) 33 C07K014-505
ADT WO 9928346 A1 **WO 1998-EP7876 19981203**; DE 19753681 A1 **DE 1997-1053681 19971203**; AU 9921581 A AU 1999-21581 19981203; EP 1037921 A1 EP 1998-965756 19981203, **WO 1998-EP7876 19981203**; ZA 9811003 A ZA 1998-11003 19981202; BR 9813391 A BR 1998-13391 19981203, **WO 1998-EP7876 19981203**; CN 1280586 A CN 1998-811792 19981203; KR 2001024681 A KR 2000-706085 20000603; JP 2001525338 W **WO 1998-EP7876 19981203**, JP 2000-523237 19981203; AU 744086 B AU 1999-21581 19981203; JP 2003238593 A Div ex JP 2000-523237 19981203, JP 2003-55499 19981203; KR 390325 B **WO 1998-EP7876 19981203**, KR 2000-706085 20000603; JP 2004339234 A Div ex JP 2000-523237 19981203, JP 2004-219290 20040727
FDT AU 9921581 A Based on WO 9928346; EP 1037921 A1 Based on WO 9928346; BR 9813391 A Based on WO 9928346; JP 2001525338 W Based on WO 9928346; AU 744086 B Previous Publ. AU 9921581, Based on WO 9928346; KR 390325 B Previous Publ. KR 2001024681, Based on WO 9928346
PRAI EP 1998-113415 19980717; **DE 1997-19753681 19971203**; ZA 1998-11003 19981202
IC ICM A61K000-00; A61K038-17; C07K014-505
ICS A61K038-18; A61P007-06; A61P043-00; C07K014-435; C12N005-06; C12N005-08; C12N005-10; C12N015-09; C12N015-16; C12N015-85; C12P021-02
ICA A61K038-22; C07K001-20; C07K001-22
AB WO 9928346 A UPAB: 20041208
NOVELTY - An erythropoietin (EPO) composition (I) consists mainly or completely of glycosylised EPO molecules and comprises at least 75% tetra-antenna structures with respect to the total N-bound carbohydrate chains present.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) (I) comprising on average 3.7 units N-acetyl-lactosamine with respect to an N-bound carbohydrate chain to an EPO molecule, and 11.1 units of N-acetyl-lactosamine with respect to the total N-glycosylation of an EPO molecules;

(2) (I) where the average product of the multiplication of N-acetyl-lactosamine/carbohydrate chain/EPO molecule times sialinic acid content is 43.3 or 130, when multiplying with N-acetyl-lactosamine/total N-glycosylation with sialinic acid;

(3) a pharmaceutical composition comprising (I) and diluents, carriers and other additives;

(4) a preparation of (I) comprising:

(a) selecting a production cell which can produce carbohydrate chains with a high content of tetra-antenna structures and/or N-acetyl-lactosamine content;

(b) selecting of culture conditions which promotes the cells of (a); and

(c) separating the undesired products from the EPO molecules chains with a high content of tetra-antenna structures and/or N-acetyl-lactosamine content; and

(5) a method for increasing the specific activity of (I), comprising concentrating (I) so that (I) has:
(a) a high content of tetra-antenna carbohydrate structures;
(b) a large number of N-acetyl-lactosamine units;
(c) a high product of N-acetyl-lactosamine units and sialinic acid;
(d) a high content of N-acetyl-lactosamine repeats; and/or
(e) a high product of N-acetyl-lactosamine repeats and tetra-antenna carbohydrate structures.
USE - (I) is used in the preparation of medicaments, which promote the production of red blood cells.
ADVANTAGE - (I) has a higher specific activity in vivo than prior art EPO molecules.
Dwg.0/3

FS CPI
FA AB; DCN
MC CPI: B04-N02; D05-C08; D05-H08

L6 ANSWER 3 OF 4 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN
AN 1999-142926 [12] WPIX
CR 1999-142925 [12]; 1999-371097 [31]
DNC C1999-041855
TI New human cells containing erythropoietin gene controlled by heterologous promoter - for large scale production of pure, glycosylated erythropoietin.
DC B04 D16
IN AUER, J; BRANDT, M; HONOLD, K; KOLLER, H; STERN, A; KOLL, H; EBERHARDT, H; FRANZE, R; WALLERIUS, C; PESSARA, U; KNOLL, H
PA (HOFF) ROCHE DIAGNOSTICS GMBH; (BOEF) BOEHRINGER MANNHEIM GMBH; (AUER-I) AUER J; (BRAN-I) BRANDT M; (HONO-I) HONOLD K; (KOLL-I) KOLL H; (STER-I) STERN A; (FRAN-I) FRANZE R; (PESS-I) PESSARA U
CYC 85
PI WO 9905268 A1 19990204 (199912)* GE 70 C12N015-12
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW

AU 9889786	A	19990216	(199926)		
EP 986644	A1	20000322	(200019) GE		C12N015-12
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE					
ZA 9806516	A	20000329	(200022)	51	A61K000-00
BR 9811031	A	20000808	(200044)		C12N015-12
CN 1265143	A	20000830	(200059)		C12N015-12
CN 1280586	A	20010117	(200128)		C07K014-505
JP 2001511343	W	20010814	(200154)	54	C12N015-09
KR 2001022107	A	20010315	(200159)		C12N015-12
KR 2001024681	A	20010326	(200161)		C07K014-505
MX 2000005048	A1	20010201	(200168)		A61K038-18
US 6391633	B1	20020521	(200239)		C12N005-06
US 2002110913	A1	20020815	(200256)		C12N005-08
AU 754619	B	20021121	(200305)		C12N015-12
JP 3394240	B2	20030407	(200327)	9	C07K014-505
US 6544748	B2	20030408	(200327)		C12Q001-68
US 6548296	B1	20030415	(200329)		C12P021-06
US 6555373	B1	20030429	(200331)		C12N005-02
US 2003166275	A1	20030904	(200359)		C12N005-08
TW 574372	A	20040201	(200453)		C12P021-02
US 2004203001	A1	20041014	(200469)		C12Q001-68

ADT WO 9905268 A1 WO 1998-EP4590 19980722; AU 9889786 A AU 1998-89786 19980722; EP 986644 A1 EP 1998-941401 19980722, WO 1998-EP4590 19980722; ZA 9806516 A ZA 1998-6516 19980722; BR 9811031 A BR 1998-11031 19980722, WO 1998-EP4590 19980722; CN 1265143 A CN 1998-807482 19980722; CN 1280586 A CN 1998-811792 19981203; JP 2001511343 W WO 1998-EP4590 19980722, JP 2000-504243 19980722; KR 2001022107 A KR 2000-700677 20000121; KR 2001024681 A KR 2000-706085 20000603; MX 2000005048 A1 MX 2000-5048 20000523; US 6391633 B1 WO 1998-EP4590 19980722, US 2000-463380 20000121; US 2002110913 A1 Cont of WO 1998-EP4590 19980722, Cont of US 2000-463380 20000121, US 2001-985357 20011102; AU 754619 B AU 1998-89786 19980722; JP 3394240 B2 WO 1998-EP7819 19981202, JP 2000-523332 19981202; US 6544748 B2

CIP of US 1998-113692 19980710, Cont of WO 1998-EP4590 19980723, Cont of US 2000-463380 20000121, US 2001-985357 20011102; US 6548296 B1 US 1998-113692 19980710; US 6555373 B1 Cont of US 1998-113692 19980710, US 2000-607277 20000630; US 2003166275 A1 CIP of US 1998-113692 19980710, Cont of WO 1998-EP4590 19980722, Cont of US 2000-463380 20000121, Cont of US 2001-985357 20011102, US 2003-353767 20030129; TW 574372 A TW 1998-116028 19980924; US 2004203001 A1 Cont of US 1998-113692 19980710, US 2003-351397 20030127

FDT AU 9889786 A Based on WO 9905268; EP 986644 A1 Based on WO 9905268; BR 9811031 A Based on WO 9905268; JP 2001511343 W Based on WO 9905268; US 6391633 B1 Based on WO 9905268; AU 754619 B Previous Publ. AU 9889786, Based on WO 9905268; JP 3394240 B2 Previous Publ. JP 200125342, Based on WO 9928455; US 6544748 B2 Cont of US 6391633; US 2003166275 A1 Cont of US 6391633, Cont of US 6544748; US 2004203001 A1 Cont of US 6548296

PRAI US 1998-113692 19980710; EP 1997-112640 19970723; **DE 1997-19753681 19971203**; EP 1998-113415 19980717; EP 1998-113409 19980717; EP 1997-121073 19971201

IC ICM A61K000-00; A61K038-18; C07K014-505; C12N005-02; C12N005-06; C12N005-08; C12N015-09; C12N015-12; C12P021-02; C12P021-06; C12Q001-68

ICS A61K038-22; A61P043-00; C07K001-16; C07K001-20; C07K001-22; C12N005-00; C12N005-16; C12N015-00; C12N015-16; C12N015-62; C12N015-64; C12N015-85; C12N015-90; C12P021-04

ICA C12N005-10

AB WO 9905268 A UPAB: 20041027

Human cells (A) containing a copy of an endogenous gene (I) for erythropoietin (EPO) linked to a heterologous promoter, functional in human cells, and capable of producing at least 200 ng EPO/million cells/24 hr are new.

Also new are: (1) human cells (B) produced from (A) by gene amplification and able to produce at least 1000 ng EPO/million cells/ 24 hr; (2) DNA construct (II) for activating an endogenous EPO gene in a human cell comprising: (i) two flanking sequences, homologous to regions (i.e. the 5'-untranslated region, exon 1 or intron 1) of the human EPO gene locus and capable of homologous recombination, including in the exon 1 region a modified sequence encoding Met-X1-X2-X3 X1 = Gly or Ser; X2 = Ala, Val, Leu, Ile, Ser or Pro; X3 = Pro, Arg, Cys or His; but X1-X2-X3 is not Gly-Val-His; (ii) a positive selection marker gene; (iii) a heterologous expression control sequence; and (iv) optionally an amplification gene; (3) DNA construct (IIa) similar to (II) without the modified exon 1 region but with the expression control sequence no more than 1.1 kb from the translation start site; (4) plasmid p189 (DSM 11661) or its derivatives; (5) isolated human EPO with specific activity, in vivo, at least 0.1 million units/mg, produced by (A) or (B) and free of urinary impurities; and (6) isolated DNA (III) encoding an EPO in which the first 4 amino acids of the signal peptide are Met-X1-X2-X3.

USE - (A) and (B) are used to produce EPO for therapeutic use (stimulation of erythrocyte production).

ADVANTAGE - The new cells make possible economical, large scale production of pure human EPO, and are significantly more productive than transformed CHO cells. Altering the signal sequence and/or the distance between promoter and start signal optimises EPO expression.

Dwg.4c/6

FS CPI

FA AB; GI

MC CPI: B04-C01; B04-E03F; B04-F02; D05-C12; D05-H12A; D05-H12B2; D05-H14B2; D05-H17A6; D05-H17B6; D05-H18B

L6 ANSWER 4 OF 4 WPIX COPYRIGHT 2005 THE THOMSON CORP on STN

AN 1999-142925 [12] WPIX

CR 1999-142926 [12]; 1999-371116 [31]

DNC C1999-041854

TI Selecting human cells for use in protein production by endogenous gene activation - for large scale production of erythropoietin.

DC B04 D16

IN AUER, J; BRANDT, M; HONOLD, K; KOLL, H; STERN, A; FRANZE, R; PESSARA, U

PA (HOFF) ROCHE DIAGNOSTICS GMBH; (BOEF) BOEHRINGER MANNHEIM GMBH; (BRAN-I) BRANDT M; (FRAN-I) FRANZE R; (PESS-I) PESSARA U; (AUER-I) AUER J; (HONO-I) HONOLD K; (KOLL-I) KOLL H; (STER-I) STERN A

CYC 85
PI WO 9905267 A1 19990204 (199912)* GE 47 C12N015-12
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9890674 A 19990216 (199926)
ZA 9806515 A 20000329 (200022) 32 C12N000-00
EP 1000154 A1 20000517 (200028) GE C12N015-12
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU NL PT SE
BR 9811542 A 20000822 (200050) C12N015-12
CN 1265143 A 20000830 (200059) C12N015-12
CN 1265144 A 20000830 (200059) C12N015-12
AU 737605 B 20010823 (200154) C12N015-12
JP 2001511342 W 20010814 (200154) 35 C12N015-09
KR 2001022107 A 20010315 (200159) C12N015-12
KR 2001022126 A 20010315 (200159) C12N015-12
MX 2000000677 A1 20001101 (200163) C07K014-505
US 6395484 B1 20020528 (200243) C12P021-06
AU 2002029337 A 20020523 (200245)# A61K038-18
US 2002164792 A1 20021107 (200275) C12N005-08
US 6548296 B1 20030415 (200329) C12P021-06
US 6555373 B1 20030429 (200331) C12N005-02
TW 574372 A 20040201 (200453) C12P021-02
US 2004203001 A1 20041014 (200469) C12Q001-68
AU 776280 B2 20040902 (200477)# C12N015-12
US 6846673 B2 20050125 (200508) C12N005-00
ADT WO 9905267 A1 WO 1998-EP4584 19980722; AU 9890674 A AU 1998-90674 19980722; ZA 9806515 A ZA 1998-6515 19980722; EP 1000154 A1 EP 1998-942592 19980722, WO 1998-EP4584 19980722; BR 9811542 A BR 1998-11542 19980722, WO 1998-EP4584 19980722; CN 1265143 A CN 1998-807482 19980722; CN 1265144 A CN 1998-807498 19980722; AU 737605 B AU 1998-90674 19980722; JP 2001511342 W WO 1998-EP4584 19980722, JP 2000-504242 19980722; KR 2001022107 A KR 2000-700677 20000121; KR 2001022126 A KR 2000-700696 20000121; MX 2000000677 A1 MX 2000-677 20000119; US 6395484 B1 Cont of US 1998-113692 19980710, WO 1998-EP4584 19980722, US 2000-463339 20000530; AU 2002029337 A Div ex AU 1998-89786 19980722, AU 2002-29337 20020328; US 2002164792 A1 Cont of WO 1998-EP4584 19980722, Cont of US 2000-463339 20000530, US 2002-112755 20020402; US 6548296 B1 US 1998-113692 19980710; US 6555373 B1 Cont of US 1998-113692 19980710, US 2000-607277 20000630; TW 574372 A TW 1998-116028 19980924; US 2004203001 A1 Cont of US 1998-113692 19980710, US 2003-351397 20030127; AU 776280 B2 Div ex AU 1998-89786 19980722, AU 2002-29337 20020328; US 6846673 B2 Cont of WO 1998-EP4584 19980722, Cont of US 2000-463339 20000530, US 2002-112755 20020402
FDT AU 9890674 A Based on WO 9905267; EP 1000154 A1 Based on WO 9905267; BR 9811542 A Based on WO 9905267; AU 737605 B Previous Publ. AU 9890674, Based on WO 9905267; JP 2001511342 W Based on WO 9905267; US 6395484 B1 Based on WO 9905267; US 2002164792 A1 Cont of US 6395484; US 2004203001 A1 Cont of US 6548296; AU 776280 B2 Previous Publ. AU 2002029337
PRAI US 1998-113692 19980710; EP 1997-112640 19970723;
EP 1997-121073 19971201; **DE 1997-19753681 19971203**; AU 2002-29337 20020328; WO 1998-EP4590 19980722
IC ICM A61K038-18; C07K014-505; C12N000-00; C12N005-00; C12N005-02; C12N005-08; C12N015-09; C12N015-12; C12P021-02; C12P021-06; C12Q001-68
ICS C12N005-06; C12N005-10; C12N015-00; C12N015-10; C12N015-62; C12N015-63; C12N015-85; C12N015-87; C12N015-90; C12P021-04
AB WO 9905267 A UPAB: 20050202
Selection of human cell lines for preparation of human proteins (I) by activation of an endogenous target gene (II) comprises testing the cell for: (i) presence of (II) with the required gene sequence; and (ii) ability to undergo at least 5 population doublings within 14 days in suspension culture and when grown in serum-free medium. If these conditions are fulfilled, the cell line is useful for endogenous activation of (II).

Also new are (1) human cell lines that contain a copy of an endogenous gene operably linked to a heterologous promoter, functional in

the cell, and able to produce at least 200 ng of the gene-encoded protein per million cell per 24 hr; and (2) human cell lines, produced by gene amplification of the cells of (1), containing many copies of the gene and able to produce at least 1000 ng protein per million cells per 24 hr.

USE - The cells are used for production of human thrombopoietin, colony-stimulating factors, blood coagulation proteins, interleukins, chemokines, neurotrophic factors, proteins that regulate bone growth, hedgehog proteins, (tumour) growth factors, adrenocorticotrophic hormone, encephalins, endorphins, receptors and other protein-binding proteins, but especially erythropoietin (EPO).

ADVANTAGE - The use of the selected cells permits production of (I) in large fermentors, economically and in a form suitable for therapeutic use. With gene amplification, yields of 5000-25000 ng (I)/million cells/24 hr can be achieved.

Dwg. 3/4

FS CPI
FA AB; GI
MC CPI: B04-N02; D05-C12; D05-H08; D05-H09; D05-H12A; D05-H14B2; D05-H17A2; D05-H18B

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